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SOMATIC AND VISCERAL CONNECTIONS OF THE DIENCEPHALON *

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The diencephalon, as all other subdivisions of the nervous system, is arbitrarily delimited, and contains within its limits a series of centers associated with various functions; these centers are not only interrelated with each other, but they are as intimately related with lower and higher segments of the nervous system. Thus the degree of differentiation of the diencephalon in any form is in direct relation with the extent of development of the peripheral nervous system and the degree of differentiation of the spinal, bulbar and pontile centers. Moreover, the possible complexity of the striatal and cortical centers is limited and determined by the complexity of the diencephalon.

A study of the phylogenetic development of the nervous system reveals a gradual increase in the longitudinal conduction pathways and a progressive differentiation through the whole extent of the nervous system, which at certain stages may involve more particularly a single segment, but which must of necessity, because of the various paths, affect to some degree all of the subdivisions. The behavior of the more primitive types of vertebrates is more stereotyped and is concerned largely with relatively direct responses to stimulation. Gradually, as the vertebrate scale is ascended, and coincident with the development of longitudinal conduction paths within the central nervous system and the specialization of nerve centers, including those of the tectum, forebrain and diencephalon, the response becomes more variable and is capable of much greater delay, as is to be seen in the behavior of mammals, and particularly of primates and man.

In this progressive development the diencephalon plays an important rôle. This brain segment is often referred to as if its only function was that of a ganglionic internode, a place of synapse for impulses passing to the cortex. There is little doubt that the vast majority of

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the nerve impulses, with the exception of the olfactory, which attain cortical centers, do so only after a relay in the dorsal part of the diencephalon. The very presence of these synapses raises the question of localization and interrelation within the diencephalic centers, and stresses the importance and the undoubted existence of modifications of the impulses within these centers. The lack of pure sensations in normal human psychology is to be expected in the absence of such anatomic connections and specific localization within the diencephalon as would provide the mechanism for such sensations. Nevertheless, just as the dorsal part of the diencephalon is a means of entrance to striatal and cortical centers, so other portions of this brain segment are equally important regions of synapse for efferent fibers from the cortex and the striatum to lower centers. In addition to these functions, this center comprises a reflex center for proprioceptive, exteroceptive and interoceptive impulses, and a conscious center for unlocalized pain. A further important series of relations of which little is known in higher forms, aside from auditory and optic centers, are those of tectodiencephalic and diencephalotegmental connections.

The thalamus provides for the affective tone of impulses, and is a primary center involved in various types of emotional expression. Irritation or injury of its various regions leads to chorea, tremor and automatic screaming and crying. Injury or irritation of the region may change the whole affective attitude of a person. Normally, this center gives the emotional content to a given response. The work of Head and Holmes indicates that the thalamus is closely tied up with affective experience and with the whole range of pleasurable and painful qualities, which are undisturbed when lesions are confined to cortical centers alone. Tilney and Riley have emphasized particularly the relation of these primitive emotional qualities to the development of personality and behavior. Pain apparently comes into consciousness in the thalamus, as is evidenced in the work of Head and Holmes, and the question of pleasure and pain from the neurologic standpoint, and the general functions of the diencephalon have been discussed by Herrick, 1926 and 1927. The work of von Bechterew, Strümpell, von Monakow, Dejerine, Head and Holmes, Jelliffe and White and others may be consulted for further accounts of the functional activity of the thalamus as this is exhibited in clinical cases.

To a study of the diencephalon there are many avenues of approach. Attention may be drawn to: clinical studies, which have contributed fundamentally to knowledge of the diencephalon; experimental observations, which have widened the horizon and indicated regions deserving of further study; anatomic descriptions, which have given the general nuclear pattern and certain fiber connections, and the comparative neurologic approach, which has contributed much to an understanding of the factors involved in the progressive development of the diencephalon

and consequently the significance of the gradual differentiation of its various parts. The following brief survey of the diencephalon is based on a comparative neurologic study of this brain segment, supplemented by a study of the literature. To any one familiar with the field it is unnecessary to state that the limits set for this contribution preclude a full consideration of the literature involved, so that only such relations and connections have been emphasized as appear to us to have special significance for the specific functional activities of this region. It may be emphasized that all adequate physiologic experimentation must have its basis in a thorough knowledge of the normal anatomy of the form on which the experiment is performed.

SUBDIVISIONS OF THE DIENCEPHALON

In the following account, the diencephalon has been divided into epithalamus, hypothalamus and thalamus, the latter being secondarily divided into a dorsal and a ventral portion. The geniculate bodies, which are sometimes classified as metathalamus, are here regarded as part of the dorsal thalamus. The ventral thalamus includes those efferent centers, below the sulcus medius, the greater part of which are grouped in ordinary terminology under the term subthalamic centers. This subdivision of the diencephalon is not in agreement with the B N A nomenclature, but is to be found with various modifications in contributions based on comparative neurologic studies. These subdivisions, unlike those of the B N A, have their basis in the phylogenetic and the functional development of this region. The major diencephalic subdivisions may be summarized as follows:

Epithalamus
Thalamus
  Dorsal thalamus including geniculates
  Ventral thalamus (subthalamus)
Hypothalamus

In the main, the epithalamus and hypothalamus are respectively olfactosomatic and olfactovisceral correlation centers for conscious and reflex responses to olfactory stimulations. The dorsal thalamus is particularly concerned with the reception of exteroceptive and proprioceptive impulses, in most cases after synapse in lower centers, and their transmission either to the striatum and cortex of the forebrain, or directly to efferent centers. The ventral thalamus is on the efferent side of the arc. It conducts impulses received from the dorsal thalamus, from the lenticular nucleus, and, to some extent, from the motor cortex to the efferent centers of the midbrain, pons, medulla and spinal cord. Epithalamic and hypothalamic centers, therefore, are concerned primarily with the reception of visceral or interoceptive impulses and their correlation and discharge to appropriate somatic and visceral efferent

centers. The dorsal and ventral thalami are concerned primarily, although not exclusively, in a similar correlation of exteroceptive and proprioceptive impulses and their discharge to the proper centers.

EPITHALAMUS AND HYPOTHALAMUS

These two diencephalic subdivisions may be considered together with profit, by reason of certain parallelisms in structural arrangement and functional activity. This is well illustrated in the following outline, in which epithalamus and hypothalamus are each divided into endocrine, olfactory and non-olfactory portions.

Epithalamus

(1) Endocrine: Epiphysis and choroid plexus of third ventricle
(2) Nonolfactory portion: Posterior commissure
(3) Olfactosomatic correlation centers: Habenular nuclei, habenular commissure and stria medullaris

Hypothalamus

(1) Endocrine: Hypophysis (pars neuralis of neural tube genesis, the remainder from oral cavity)
(2) Nonolfactory portion: Pars optica hypothalami, mainly chiasma and supra-optic commissure
(3) Olfactovisceral correlation centers: Corpora mammillaria, tuber cinereum and associated hypothalamic gray matter.

For the moment we are not concerned with glands of internal secretion and will attempt no discussion of them. However, it is worthy of note that here, as elsewhere in the nervous system, regions not directly concerned with the conduction of nervous impulses frequently acquire secondarily secretory function. The nonolfactory components of the epithalamus and hypothalamus are made up largely of fiber bundles, decussating and commissural in character, which in the main connect regions outside of the epithalamic and hypothalamic areas.

Nonolfactory Components.—The posterior commissure, the nonolfactory component of the epithalamus, lies at the boundary line between the diencephalon and mesencephalon and is sometimes regarded as belonging entirely to the latter segment. In reptiles and birds, in which the pretectal and tectal centers are highly developed, this commissure is correspondingly large. In these forms it consists of two major divisions, a dorsal division providing commissural connections between the optic tecta and a ventral division carrying commissural and decussating fibers between pretectal and inferior collicular (corpus posticum) centers and fibers from associated nuclei of the commissure. Furthermore, in reptiles it has been demonstrated that this commissure transmits fibers arising in the nucleus of the median longitudinal fasciculus of one side and passing to the corresponding fasciculus of the other side. In mammals, and particularly in higher mammals and man,

the posterior commissure is greatly reduced. In these forms it is known to interconnect the superior colliculi of the two sides. Fibers which course in it to the posterior thalamic regions are probably the remnants of the phylogenetically old, pretecal connections. There is reason to believe that in mammals, as in lower forms, fibers from the nucleus of the median longitudinal fasciculus cross to the contralateral fasciculus by way of this commissure, but this needs confirmation in higher mammals and man. So far as our knowledge goes, there is no trace of the inferior collicular connections known for reptiles and birds. All the evidence indicates that the posterior commissure is a dependency of the tectal, pretectal and subtectal regions of the vertebrate brain, and that it increases or decreases as these areas increase or decrease.

The optic chiasma, one of the main fiber bundles of the nonolfactory portion of the hypothalamus, is composed of decussating and nondecussating fibers extending between the retina and the dorsal thalamus, the tectum and tegmentum of the midbrain. This important system of fiber bundles will be given further consideration in the discussion of the optic portion of the dorsal thalamus.

Crossing in the chiasmal ridge at the level of the optic decussation and immediately behind it are found the supra-optic or postoptic commissural systems. These consist of three main portions, capable of further subdivision and variously designated in the literature. The division most ventrally placed and in mammals, where it is usually medullated, frequently indistinguishable from the optic tract, is Gudden's or the ventral supra-optic or ventral postoptic commissure, connecting the medial geniculate bodies of the two sides and to some extent the inferior colliculi. Comparative neurologists have demonstrated this fiber system in amphibians, reptiles, birds and mammals (fig. 1). Larsell described a commissura transversa in the frog which he considered comparable with the mammalian commissure of Gudden.

The second of the supra-optic or postoptic commissural systems is most frequently designated as Meynert's commissure. It is a relatively complex system of fibers with no single nucleus of origin and no single nucleus of termination. The postoptic system, described by Herrick (1917) for Necturus, is probably the forerunner of both Gudden's and Meynert's commissures as found in higher forms. It may contain representatives of Ganser's as well. Herrick showed that the postoptic system is complex in *Urodeles*. It consists of two main divisions. The first, tractus tectothalamicus et hypothalamicus cruciatus, has anterior and posterior divisions which are related to areas homologous with the mammalian superior colliculi. These distribute fibers, after decussation, to the ventral thalamus, hypothalamus and the nucleus of the tuberculum posterius. Certain unmedullated fibers from the superior colliculus, after decussation, appear to distribute to the pars optica thalami. The

second division, tractus thalamohypothalamicus et peduncularis cruciatus, arises in the pars dorsalis thalami, and after decussation terminates in the ventral part of the thalamus and the region of the cerebral peduncle. Our own observations on reptiles confirm in a general way these observations on amphibians, but show in Meynert's commissure (*1*) a significant increase in the intertectal and tectothalamic fibers, associated

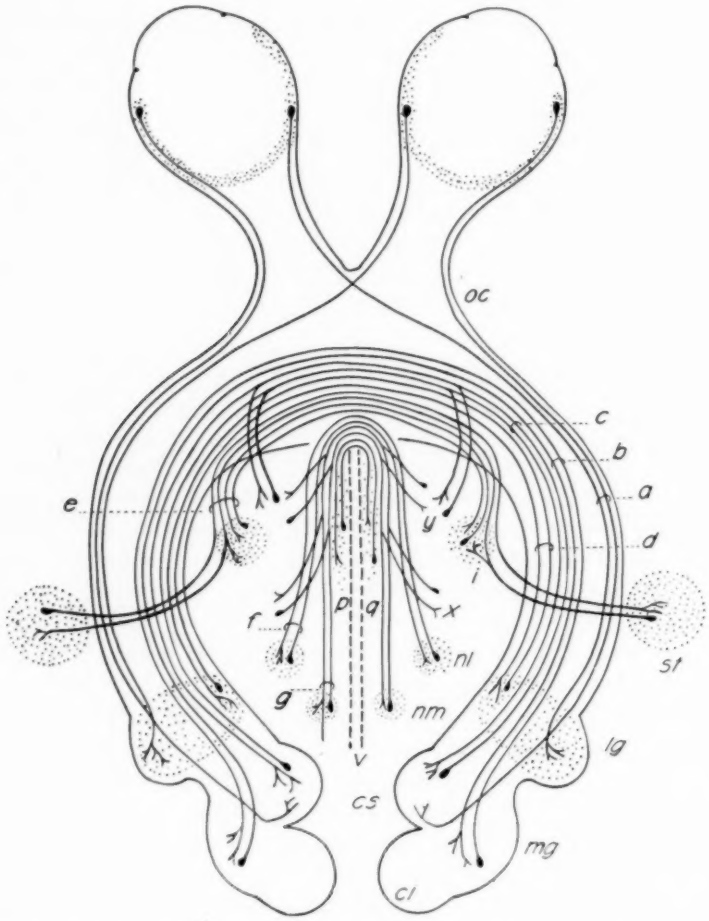

Fig. 1.—Supra-optic systems: *a*, optic fibers; *b*, Gudden's commissure; *c*, superior collicular component of Meynert's commissure; *ci*, inferior colliculus; *cs*, superior colliculus; *d*, intergeniculate fibers; *e*, striatal component of Meynert's commissure; *f*, subthalamic component of Forel's commissure; *g*, median longitudinal fascicular component of Ganser's commissure; *i*, represents subthalamic areas; *lg*, lateral geniculate; *mg*, median geniculate; *nl*, nucleus Luysi or subthalamic nucleus; *nm*, nucleus median longitudinal fasciculus; *oc*, optic chiasma; *pg*, periventricular gray and fibers; *st*, striatum; *v*, ventricle; *x* and *y*, hypothalamic and ventral thalamic gray. Forel's commissure is the supramammillary commissure.

with the presence of a more highly developed reptilian tectum and (*2*) an intermingling and synaptic relation of this system with the forebrain paths. In birds, our own unpublished observations confirm and extend earlier statements with regard to this commissure. They indicate, as various neurologists have contended, that in avian forms there are fibers from the striatal region of one hemisphere to the homolateral and contralateral ventral thalamus, and to the contralateral striatum. Still the system shows great similarity to the fibers in reptiles. In higher mammals, with the relative reduction of the tectum as compared with that of reptiles and birds and with the reduction of the striatum as contrasted with that of avian forms, Meynert's commissure forms a proportionately less prominent fiber bundle. Yet in mammals it is still a complex system with all of the components which it has acquired in phylogeny. Certain of its more prominent bundles are illustrated in figure 1 and may be listed as follows: *c*, tectal fibers associating the superior colliculus with the contralateral ventral thalamus; *d*, intergeniculate fibers which pass from one lateral geniculate to the other and are probably not present in all mammals; *e*, fibers connecting one lenticular nucleus with that of the other side and with subthalamic regions. We are better acquainted with this fiber system in submammalian forms, and it is probable that there are present certain other significant connections in higher forms not included in this list. As regards its components, there is no general agreement in the literature. Some workers, among them Wallenberg, regard it as carrying decussating lemnisci fibers; certain writers have confirmed (Tsai) and others denied (Dejerine) its relation to subthalamic nuclei. Foix and Nicolesco, in their comprehensive recent account of the thalamus, listed, with other connections of Meynert's commissure, a connection with the substantia innominata of Reichert. It is evident that further investigation is required to give an adequate understanding of this system, in spite of the great amount of work which has been done on it.

The third member of the supra-optic commissural system is Ganser's commissure, in part at least also known as fibrae ansulatae. In this commissure course fibers which interconnect the subthalamic or ventral thalamic regions of the two sides, as has been shown by Tsai for marsupials and by Gurdjian for rodents. The periventricular gray in the region caudal to the chiasma is likewise connected by fibers of this commissure. In it course also fibers which arise in the nucleus of the median longitudinal fasciculus of one side and pass to the contralateral nucleus and possibly directly to the median longitudinal fasciculus of the other side. The fibers to the nucleus of the fasciculus were described for Varanus by Beccari and are evident in our material of *Alligator mississippiensis* (Huber and Crosby). We believe them to be present in birds and mammals. The components of Ganser's com-

missure are shown in figure 1, *x* and *y* indicating the subthalamic component; *g*, the median longitudinal fasciculus component and *p g*, the periventricular component.

Olfactory Component.—The habenula of the epithalamus and the mammillary body of the hypothalamus show certain resemblances in structure and fiber connections which are emphasized in the accompany-

- Epithalamus (olfactosomatic correlation center)
  - Into habenula
    - Corticohabenular
    - Olfactohabenular (stria medullaris)
    - Thalamohabenular
    - Tectohabenular
  - Out of habenula
    - Habenulodiencephalic (thalamic)
    - Habenulotegmental (dorsal tegmental nucleus)
    - Habenulopeduncular (interpeduncular nucleus)
- Hypothalamus (olfactovisceral correlation center)
  - Into mammillary body
    - Corticomammillary (fornix)
    - Olfactomammillary (anterior perforated space)
    - Cineromammillary (hypothalamomammillary)
    - Mammillohypothalamic (tuber cinereum)
    - Mammillary peduncle
  - Out of mammillary body
    - Mammillothalamic (Vicq d'Azyr)
    - Mammillotegmental (dorsal tegmental nucleus)
    - Mammillopeduncular (interpeduncular nucleus)

ing outline. The following account is based on avian and particularly on general mammalian relations; especial points in human beings will be stressed.

The habenula consists in birds and mammals, including man, of two nuclei: an internal one containing medium sized, rather closely packed neurons, and an external one composed usually of more scattered cells. In the majority of mammals the mammillary body likewise has an internal and an external nucleus. In man the latter is greatly reduced; it is more or less fused with the so-called mammillo-infundibular nucleus and it is sometimes regarded as absent. Olfactory impulses entering the olfactory bulb by way of neuraxes from the olfactory epithelium of the nasal cavity distribute, after synapse, as interbulbar fibers to the bulb

of the opposite side (fig. 2 *a*), and to the medial olfactory area (including gyrus subcallosus) and the lateral olfactory area of the anterior perforated space. From the medial olfactory area, the gyrus subcallosus, the preoptic area, and the amygdaloid nucleus neurons of the next order send their neuraxes to the habenula, all entering it by way of the stria medullaris and appearing to distribute chiefly to its internal nucleus. Other fibers, either with or without a synapse in the medial olfactory area, pass to the septum or to the gray striae of Lancisius which overlie

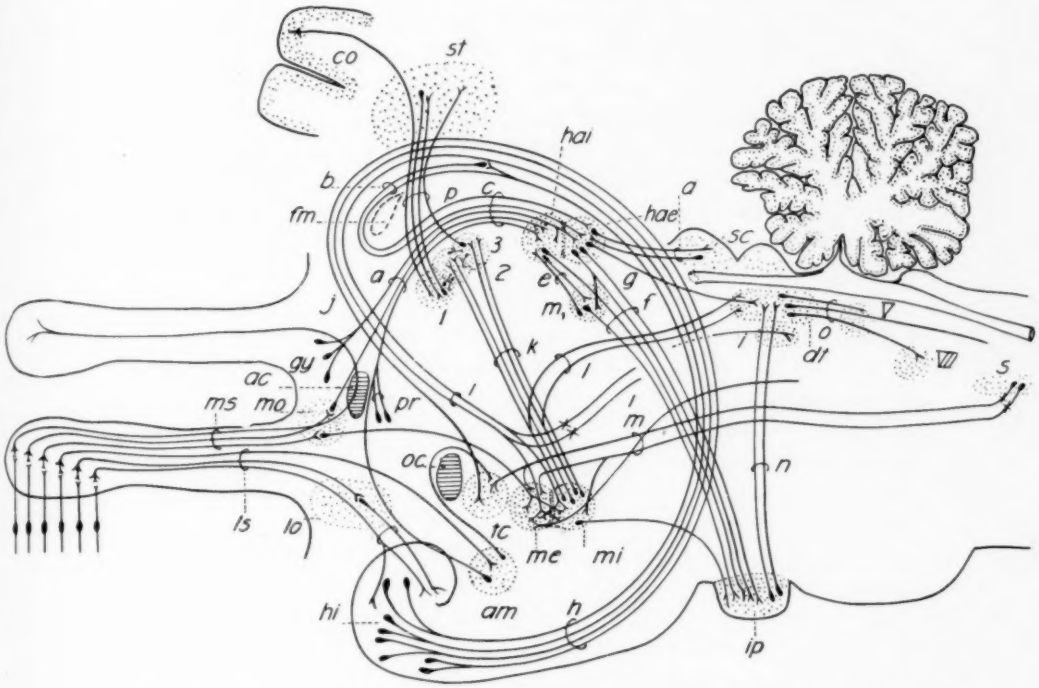

FIG. 2.—Olfactory connections of the diencephalon: *a*, olfactohabenular fibers; *ac*, anterior commissure; *am*, amygdaloid nucleus; *b*, septohabenular and corticohabenular tract; *c*, stria medullaris; *co*, cortex; *d*, tectohabenular and habenulotectal fibers; *dt*, dorsal tegmental nucleus; *e*, habenulodiencephalic and thalamohabenular fibers; *f*, habenulopeduncular fibers; *fm*, foramen of Monro; *g*, habenulotegmental fibers; *gy*, gyrus subcallosus; *h*, fimbria; *hae*, external habenular nucleus; *hai*, internal habenular nucleus; *hi*, hippocampus; *i*, fornix; *ip*, interpeduncular nucleus; *j*, corticohypothalamic (and septohypothalamic) fibers; *k*, mammillothalamic fibers; *l*, mammillotegmental fibers; *lo*, lateral olfactory area; *ls*, lateral olfactory stria; *m*, mammillary peduncle; m_1, nucleus of Meynert's habenulopeduncular tract; *me*, external mammillary nucleus; *mi*, internal mammillary nucleus; *mo*, medial olfactory area; *ms*, medial olfactory stria; *n*, pedunculotegmental fibers; *o*, dorsal longitudinal fasciculus of Schütze; *oc*, optic chiasma; *pr*, preoptic area; *s*, bulbar centers; *sc*, superior colliculus; *st*, striatum; *tc*, tuber cinereum; *V*, motor nucleus of the fifth nerve; *VII*, motor nucleus of the seventh nerve; *1*, anterior dorsal nucleus; *2*, anterior medial nucleus; *3*, anterior ventral nucleus.

the corpus callosum and are regarded as the forward continuation of the hippocampus. They are not illustrated in the figure since we are here primarily concerned with diencephalic relations. Olfactory impulses from the bulb reach the amygdaloid nucleus and the hippocampus in the temporal lobe region, either directly from the bulb or after a synapse in the lateral olfactory area. From the hippocampus they pass by way of the fimbria and posterior pillars and body of the fornix to the level of the interventricular foramen. In their course along the septum, they are in synaptic relations with neurons of the area and are joined by fibers from it. At the level of the foramen, fibers of the bundle swing caudalward to reach the habenula by way of the stria medullaris (fig. 2 *c*). This component of the stria medullaris carries septohabenular and, we believe, corticohabenular fibers. The presence of a corticohabenular system has been denied by certain other observers (Ramon and Cajal). The corticohabenular and septohabenular components are particularly related to the external nucleus. Further work needs to be done on the details of the termination of the stria medullaris components within the habenula. After the entrance of the corticohabenular and the septohabenular systems into the stria medullaris, the remaining and larger portion of the fornix system swings ventrocaudad to the hypothalamic region as the anterior pillars (fig. 2 *i*). A part of the fibers, corticohypothalamic and septohypothalamic in nature, according to Gurdjian, distribute to the hypothalamic regions in front of the mammillary body. A varying proportion of the fibers, depending on the mammal studied, distribute to the internal and external nuclei of the mammillary body. Still other fibers decussate in the supramammillary decussation and course caudad and dorsad into the tegmental region of the midbrain, where their final distribution is as yet unknown. Many observers have contributed to our knowledge of the fornix system in mammals, among whom may be especially mentioned Edinger and Wallenberg and Cajal (1911). Connections have also been described from the amygdaloid nucleus to the hypothalamus; these will be considered later. Thus the habenula and the mammillary nuclei receive impulses from both basal and cortical olfactory centers.

In birds, the external habenular nucleus is connected with the tectum by a fiber bundle which possibly carries impulses in both directions, thus providing habenulotectal and tectohabenular connections. By means of the latter, optic and, to a certain degree, other exteroceptive impulses may be carried forward to the habenula. Likewise, the more posterior portion of the dorsal thalamus, corresponding possibly to the nucleus along the tract in mammals, is in synaptic relation with the internal habenular nucleus by way of habenulodiencephalic and thalamohabenular fibers. The latter system, which is nonmedullated in birds, but which is prominent there even in the presence of a relatively small habenula, has

in all probability representatives in mammals. Edinger described a habenulodiencephalic path. Whether the mammalian nucleus parafascicularis (fig. 2 *m*) or, as it is sometimes known, the nucleus of Meynert's tract, is the homolog of this avian nucleus still requires demonstration. The thalamohabenular fibers, through the interrelation of their nucleus with other dorsal thalamic centers, are able to carry to the habenula exteroceptive impulses perhaps particularly pain and temperature, possibly tactile as well. Thus this center becomes an olfactosomatic correlation center. The thalamohabenular and habenulodiencephalic fibers are associated with the habenulopeduncular system or, as it is frequently termed, the tractus retroflexus of Meynert. This bundle is phylogenetically old, being well developed in many lower forms. It is relatively large even in avian forms where the olfactory system is not highly developed and the stria medullaris is small, indicating that it is concerned in the discharge of other impulses as well as olfactory. In the dove it consists of two bundles, a medullated one arising from the external and an unmedullated one from the internal habenular nucleus. The medullated bundle carries with it, on the lateral side, the tectohabenular (and habenulotectal?) fibers. Some few of its fibers terminate, in relation with the associated nucleus of the habenulopeduncular tract, as habenothalamic fibers, but the greater number swing ventromediad to pass to the interpeduncular nucleus. The medial habenulopeduncular carries with it many habenulodiencephalic and thalamohabenular fibers, which synapse in the nucleus of the tract. The main bundle, joined by fibers arising in this associated nucleus, courses ventrad and likewise enters the interpeduncular nucleus (fig. 2 *f* and 1 *p*). The nucleus of the habenulopeduncular tract is situated in the dorsal thalamus. Probably it is not the homolog of the mammalian nucleus parafascicularis (d'Hollander) or nucleus of the tract of Meynert. The details of the connections in birds will be published shortly in an account of the avian forebrain and diencephalon.

The detailed relations of the habenulopeduncular tract are somewhat less understood for mammals. Both internal and external habenular nuclei are known to contribute fibers to it. As it passes through the dorsal thalamus near the posterior end of the medial nucleus, it is partly surrounded by the parafascicular nucleus (nucleus of the tract of Meynert). The majority of investigators at least fail to note whether or not the tract is in synaptic relation with this nucleus. We are inclined to believe that there is a synapse in the gray of the region and have suggested the possibility of such a relation in figure 2 m_1. The curious terminations of the habenulopeduncular tract within the interpeduncular nucleus have been noted by various observers and have been particularly well described by Cajal (1911) whose figures show the decussation and looping back of these fiber bundles within the nucleus in question. In

many animals a small fiber tract—tractus habenulotegmentalis—connects the habenula with the dorsal tegmental region (fig. 2 *d*).

As will be evident from the later discussion, the mammillary nuclei are interconnected with the hypothalamic nuclei. They likewise are in relation with the mammillary peduncle (fig. 2 *m*). With regard to the origin and the direction of conduction of the fibers of this peduncle, there has been much difference of opinion. It will be possible to quote here only representative points of view. Thus, Kölliker and Dejerine described it as a descending pathway from the external mammillary nucleus to the dorsal (von Kölliker), or to both dorsal and ventral (Dejerine) tegmental nuclei. Winkler likewise regarded it as a descending path from the external mammillary nucleus, considering that the fibers joined the medial lemniscus in the midbrain region. Forel, Wallenberg (1899) and certain others regarded the bundle as one of the constituents of the medial lemniscus, which becomes detached from the main lemnisci system and terminates in the mammillary nuclei. Edinger and Wallenberg, however, believed that the bundle is joined by fibers from the tegmental region of the midbrain. Wallenberg (1900), and later Edinger and Wallenberg, found degenerated fibers in the contralateral mammillary peduncle as well as in the medial lemniscus after destruction of the nuclei of the posterior columns (the neighboring gray was undoubtedly involved also), so that they believed this peduncle contained, in part, ascending fibers from the contralateral bulbar centers. Cajal (1911), who studied the mammillary peduncle in the mouse, rabbit and cat, came to the conclusion that the pathway consists of a principal and an accessory bundle, of which only the latter is associated with the medial lemniscus. As the bundles swing toward the mammillary body, they become incorporated into the mammillary peduncle, which courses downward and inward toward the external mammillary nucleus. According to this observer, the peduncle bifurcates as it passes toward the mammillary body, forming an anterior and a posterior branch. For the details of their distribution reference should be made to the work of Cajal (1911). For our purpose it is sufficient to state that he regarded the mammillary peduncle as an ascending path carrying nervous impulses to the external and internal mammillary nuclei and to the tuber cinereum cephalad to them. Cajal emphasized that the origin of the fibers was unknown, but suggested as a possibility that they might carry gustatory impulses.

Papez, by section of the mammillary peduncle in rat near its pontile end, produced evidence that it degenerated in an ascending direction and was to be regarded as terminating in the mammillary body. Thus his work was a confirmation of that of Cajal, but in disagreement with that of Kölliker and Dejerine and, as Papez himself stated, with the results

of Schipoff, a student in Bechterew's laboratory, who studied the tract in the dog. Papez, however, did not ascertain the origin of the bundle.

Negative evidence of the presence of gustatory fibers in the mammillary peduncle appears to be offered by the recent experimental work of Allan on the cat. In destruction of all except the extreme cephalic end of the gustatory portion of the nucleus tractus solitarii and of the upper half of the general visceral part of the nucleus of that tract, he did not produce any lesions in the corpora mammillaria or tuber cinereum, although many degenerated fibers were traced to the ventral nucleus of the thalamus. He found minute black granules in the mammillary peduncle and also in the optic tract, but disregarded them because of their size and their presence in all of his Marchi material. Section of the medial lemniscus in the inferior collicular region produced chromatolysis of the cephalic half of the general visceral portion and in the gustatory portion of the nucleus tractus solitarii. Allan's results would appear to indicate that gustatory fibers run in the medial lemniscus or, in his own words, "in adjacent fibers." Since the lesions showing chromatolysis were made at inferior collicular levels, the question as to whether or not adjacent fibers might include the mammillary peduncle appears justifiable. Allan's evidence for the presence of gustatory fibers in the medial lemniscus appears convincing, his elimination of ascending fibers of the system, by way of a mammillary peduncle component of the medial lemniscus to the mammillary body, is to our mind less convincing and needs further confirmation. It is scarcely necessary to say that the mammillary peduncle is not yet understood and that before final statements can be made further investigations, preferably of an experimental nature, are essential. In our opinion the evidence at present suggests: (*1*) that the mammillary peduncle is ascending in character (since destruction of the mammillary body produces no degeneration within it [Papez]; (*2*) that it is composed of two bundles, the principal and accessory bundles of Cajal; (*3*) that as yet there is no evidence as to the origin or function of the principal bundle, although various observations suggest that it may be in relation with the tegmental nuclei (fig. 2 *m*, the upper fiber of the peduncle); (*4*) that the accessory bundle arises at least from the contralateral regions of the bulb at or near the plane of origin of the medial lemniscus, since injuries at that level produce degenerations in the mammillary peduncle of the opposite side (Wallenberg, 1900), and (*5*) that its nucleus of origin is probably a secondary or tertiary afferent center, but that its location is not definitely known (fig. 2 *s* and the two lower fibers of the mammillary peduncle). In lower forms, particularly in fishes (Herrick, 1905), gustatory fibers have been traced from the gustatory centers of the medulla forward to a nucleus near the isthmus region, where they synapse. This secondary gustatory nucleus gives rise to fibers which pass to hypo-

thalamic regions. Thus the hypothalamus is an olfactovisceral (gustatory) center. In higher forms, such as mammals, there is considerable clinical and experimental evidence that the tuber cinereum is concerned with visceral functions. Both it and the mammillary body receive olfactory impulses, and this portion of the brain is again an olfactovisceral correlation center, although probably not in the same sense as in fishes.

The fibers of the mammillothalamic and mammillotegmental tracts arise, according to Cajal, as bifurcations of single neuraxes, from cell bodies within the mammillary nuclei. The neuraxes pass dorsad and then divide by a Y or T-shaped division, one prong passing to the mammillotegmental and one to the mammillothalamic tract. Such bifurcating fibers are joined (Gurdjian) by smaller nondividing fibers which run in the mammillothalamic division of the bundle. According to Cajal, the bundle arises from both mammillary nuclei, while Gurdjian was able to demonstrate its origin only from the internal nucleus. There may be variations in different forms. The mammillotegmental tract terminates in the dorsal tegmental nucleus the mammillothalamic within the anterior nuclei of the thalamus, particularly its anterior medial nucleus, but to some extent in its anterior ventral and possibly in its anterior dorsalis (with regard to the latter connection there is difference of opinion).

Thus far, impulses have been traced from habenula and from mammillary body to the dorsal tegmental nucleus and to the interpeduncular nucleus. From this last cell mass the impulses are relayed to the dorsal tegmental region by way of the pedunculotegmental tract (Cajal, Dejerine and others). The discharge path from the dorsal tegmental nucleus is the dorsal longitudinal fasciculus of Schütze (Dejerine and others), which carries impulses to the motor nuclei of the fifth and seventh nerves, and probably to general visceral efferent centers of the bulb.

Hypothalamic Areas.—Along the ventral surface of the brain and the ventral part of the ventricle wall, between the level of the anterior commissure and that of the mammillary body, is a more or less continuous sheet of gray matter capable, however, of secondary delimitation into nuclear groups. This whole area comprises the preoptic and hypothalamic regions. The former belongs to the telencephalon, rather than to the diencephalon, but is so related to the hypothalamic areas that it is best to consider it with them.

There is no general agreement with regard to the nomenclature of the nuclear group. In the preoptic area the ventricle wall is bordered by a narrow band of periventricular gray. This is present in lower forms such as birds. It is evident in mammals, though the clearness with which it is differentiable varies with different animals. External to the periventricular layer is the medial preoptic nucleus, and still

further lateralward the lateral preoptic center. These are present in birds and various mammals. In the hypothalamic region, Cajal differentiated a nucleus tangentialis in close relation to the optic fibers, a subventricular nucleus (noyau sous ventriculaire), and three nuclei which he regarded as belonging to the tuber cinereum in the strict sense of the word. These nuclei he termed nucleus principalis or anterior, nucleus superior and nucleus posterior. He was able to contribute somewhat to their fiber connections, for he traced into the area of the tuber cinereum some few fibers of the mammillary peduncle; to the anterior nucleus he carried stria terminalis and fibers from the capsule of the mammillary body. Cajal worked on the rabbit, mouse and rat. A more recent account of the hypothalamic region in the rat and considerable detail as to the fiber connections of the various nuclei is to be found in the paper of Gurdjian on the diencephalon. In most essentials his results agreed with those of Cajal. He divided the hypothalamic region into a series of nuclei for the detailed relations of which the original paper should be consulted. In general, his results are as follows: Immediately behind the medial preoptic area is a poorly defined but relatively large nuclear mass capable probably of secondary divisions, which he terms the anterior hypothalamic area. Ventral to this area is a small nucleus ovidus which is probably the nucleus suprachiasmaticus of certain other observers, and along the optic chiasma is the nucleus tangentialis of Cajal. As the optic fibers disappear from the midline, the nucleus supra-opticus appears in the course of Ganser's commissure. Beginning external to the anterior hypothalamic nucleus and not sharply delimited cephalad from the lateral preoptic nucleus is the nucleus hypothalamicus lateralis. This scattered cell mass extends throughout practically the extent of the hypothalamus, always maintaining its lateral position, in relation to the median forebrain bundle. Immediately caudad to the anterior hypothalamic nucleus and medial to the lateral hypothalamic nucleus, the gray of the region differentiates into further nuclear groups, nuclei hypothalamicus ventro medialis, dorsomedialis and posterior. At this level Gurdjian identified a filiform nucleus. These nuclei disappear at some slight distance in front of the mamillary body and the dorsal and ventral premammillary nuclei, the former in relation with the medial hypothalamic area and the latter with the lateral hypothalamic nucleus, appear. Internal to the medial groups of hypothalamic gray and lying close to the ventricle are the anterior and posterior periventricular nuclei. Attention is called to figure 3 in which are diagrammed the hypothalamic nuclei. The Gurdjian nomenclature has been followed more nearly in this diagram than that of any other worker. This choice of terminology depends partly on a greater personal familiarity with the results, since the work was done in this laboratory, and partly on the usefulness from the standpoint of diagram

of his more detailed account of the fiber connections of the region. The ventromedial nucleus of Gurdjian is evidently the homolog of the principal nucleus of Cajal. The dorsomedial and posterior nuclei of the former are probably in part the homologs of the superior nucleus of the tuber cinereum of the latter worker, while the dorsal premammillary nucleus at least falls within the posterior nucleus of Cajal. Further homologies of the nuclear masses in these two studies are at present uncertain.

Studies of the hypothalamic region in higher mammals have been made by a number of observers, and excellent accounts of the cytoarchitectonic and myeloarchitectonic structure in primates, including man, are to be found in the literature. Unfortunately, the majority of

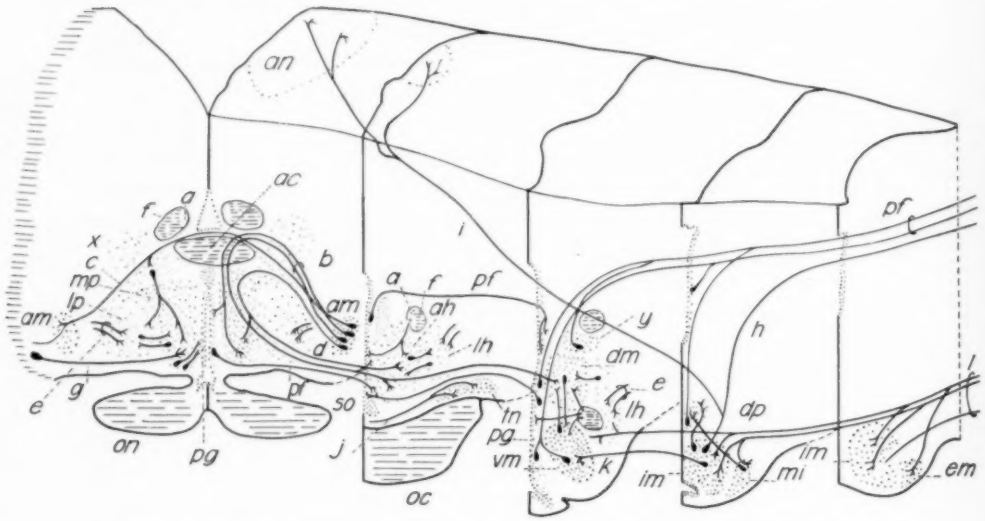

FIG. 3.—Fiber connections of the preoptic area and the tuber cinereum: *a*, corticohypothalamic and septohypothalamic tract; *ac*, anterior commissure; *am*, amygdaloid nucleus; *an*, anterior thalamic nucleus; *b*, supra-optic component of stria terminalis; *c*, commissural component of stria terminalis; *d*, preoptic component of stria terminalis; *dm*, dorsomedial hypothalamic nucleus; *dp*, dorsal premammillary nucleus; *e*, medial forebrain bundle; *em*, external mammillary nucleus; *f*, fornix; *g*, pyriform lobe and preoptic connections; *h*, mammillotegmental fibers; *i*, mammillothalamic fibers; *im*, internal mammillary nucleus; *j*, fibers of Meynert's commissure; *k*, mammillohypothalamic fibers; *l*, mammillary peduncle; *lh*, lateral hypothalamic nucleus; *lp*, lateral preoptic area; *mi*, mammilloinfundibular nucleus; *mp*, medial preoptic area; *oc*, optic chiasma; *on*, optic nerve; *pg*, periventricular gray; *so*, supra-optic nucleus; *tn*, tangential nucleus; *vm*, ventromedial hypothalamic nucleus; *x*, prethalamic nucleus; *y*, posterior hypothalamic nucleus.

these give few if any fiber connections, a state of affairs which increases the difficulty of establishing definite homologies and does not contribute to a knowledge of the function of the region, although it adds to a knowl-

edge of its structure. Certain nuclei, however, have been identified by numerous observers; among these are the tangential or perichiasmatic nucleus (Malone; Cajal; Friedemann; Spiegel and Zweig and others), and the basal optic ganglion (Winkler and Potter, 1914); the mammillo-infundibular, to some extent the equivalent of the ventral premammillary nucleus (Malone, Gurdjian and others) and the nucleus suprachiasmaticus (Spiegel and Zweig, nucleus ovoidus of Gurdjian). The gray of the tuber itself has been variously divided. For a detailed account of the nuclear masses in the region, the original papers should be consulted.

Cajal carried stria terminalis fibers (taenia semicircularis) to the principal and superior, and with less certainty to the posterior, nucleus of the tuber. The distribution of the system, as given by Gurdjian, agrees substantially with this, although contributing more in detail. The latter observer carried both preoptic and supra-optic and supracommissural components of the stria to ovoidus and the anterior hypothalamic area, and the supracommissural portion likewise to the ventromedial and dorsomedial hypothalamic areas and to the nucleus hypothalamicus periventricularis anterior. Cajal described a connection from the septum to the principal and presumably the posterior or accessory nucleus of the tuber. This is comparable, but not entirely equivalent, to the medial forebrain connections described by Gurdjian for the posterior, lateral, ventromedial and dorsomedial hypothalamic nuclei. Coursing with the fornix bundle for part of their path, in the rat at least, are fibers from the hippocampus and the amygdaloid region, termed medial corticohypothalamic and amygdalohypothalamic fibers. They supply fibers to the medial group of hypothalamic nuclei, external to the periventricular gray and to the posterior hypothalamic periventricular gray (fig. 3 *a*). According to Cajal and others, the tangential nucleus receives fibers of Meynert's dorsal supra-optic decussation (fig. 3 *j*). Gurdjian regarded his nucleus supra-opticus diffusus as possibly a bed nucleus for Ganser's commissure; his dorsal premammillary is connected with its fellow of the opposite side and with the medial mammillary nucleus. Wallenberg (1899), Cajal, Papez and Gurdjian carried fibers of the mammillary peduncle forward to the tuber cinereum region. Papez believed that they terminate in the lateral hypothalamic nucleus. They are likewise carried to the dorsal premammillary in the diagram, where it is belived they also terminate. According to Gurdjian, the lateral, the posterior and the dorsomedial hypothalamic nuclei contribute fibers to the periventricular system, as do likewise the ventral premammillary and both dorsal and ventral divisions of the posterior periventricular nucleus. Cajal emphasized connections between the mammillary nucleus and the principal (ventromedial hypothalamic) nucleus. In addition to these

fibers, various connections are made with subthalamic centers. Moreover, impulses from the dorsal thalamus, either directly or by way of a synapse in ventral or subthalamic centers, undoubtedly reach these areas. According to various observers (Foix and Nicolesco and others), ansa lenticularis fibers reach the tuber cinereum region. Part of such fibers at least appear to terminate directly in the periventricular gray. These connections may be summarized briefly as follows: the tuber cinereum region receives incoming impulses from the olfactosomatic correlation centers, the nucleus amygdalae, by way of the stria terminalis and the medial amygdalohypothalamic tract, from the olfactory cortex of the hemisphere by the medial corticohypothalamic tract and from the basal olfactory areas, including the parolfactory or septal nuclei, through the medial forebrain bundle. Nervous impulses, of a character as yet not definitely known, reach the area from lower, and probably contralateral bulbar centers, by way of the mammillary peduncle. The discharge path appears to in part indirectly by way of subthalamic centers, but particularly through a periventricular system which connects the hypothalamic and preoptic visceral regions with the midline areas of the dorsal thalamus, and particularly with the tectal and dorsal tegmental region and perhaps with areas further caudad. From the tectal areas by way of tectobulbar and spinal paths and from the dorsal tegmental nucleus by way of the dorsal longitudinal fasciculus impulses pass to somatic efferent and particularly visceral efferent centers of brain and cord.

DORSAL THALAMUS

The dorsal thalamus is divided into lateral and medial portions by the internal medullary lamina. To the medial division belong the anterior and medial nuclear groups and the nuclei of the midline. In the lateral portion are the lateral and ventral thalamic nuclei with their various subdivisions, the posterior nucleus, the pulvinar, the medial and lateral geniculate nuclei, the pretectal nucleus and certain smaller groups which will not be discussed here.

Anterior Nuclei.—The anterior portion is divided usually into three nuclei, which have received various designations and to which we are applying the names of anterior dorsal, anterior ventral and anterior medial. These three nuclei lie in the dorsal cephalic portion of the thalamus. In general, their relative position with reference to each other is indicated by their names, but this varies somewhat with different mammals. The anterior ventral and the anterior medial receive the mammillothalamic tract. According to Cajal, fibers from this bundle also reach the anterior dorsal nucleus. The anterior dorsal and the anterior ventral are connected with the cortex by way of the anterior

thalamic radiations. The accounts of these fibers in the literature suggest that the impulses may pass in both directions, although particular emphasis has been laid on the corticothalamic path (Dejerine). Commissural fibers interconnect these nuclei with their fellows of the opposite side, and internuclear fibers associate them with each other and with the adjoining lateral and medial nuclei of the thalamus. Fibers

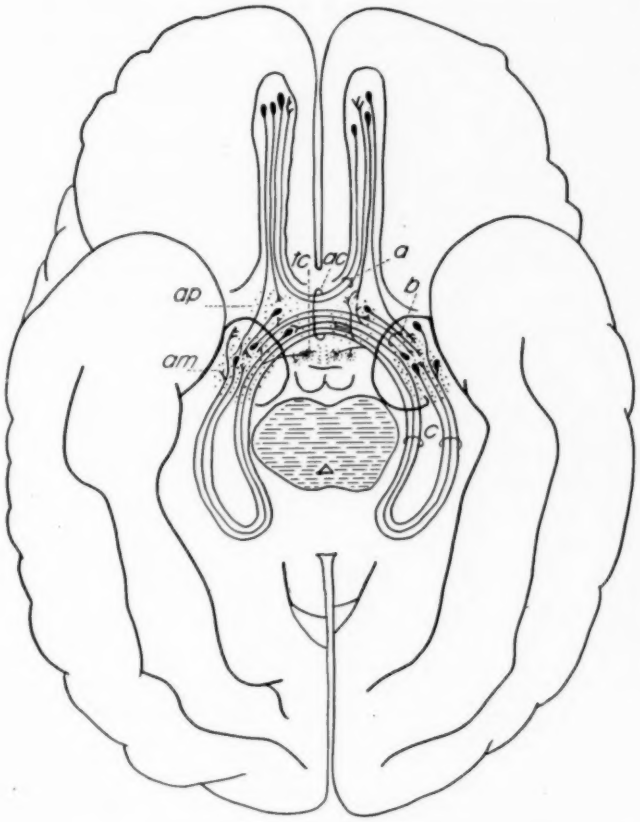

FIG. 4.—Components of the anterior commissure: *a*, interbulbar component of the anterior commissure; *ac*, anterior commissure; *am*, amygdaloid nucleus; *ap*, anterior perforated space; *b*, intertemporal component of the anterior commissure; *c*, stria terminalis component of the anterior commissure; *tc*, tuber cinereum.

from these anterior nuclei, and more particularly from the anterior ventral group, pass to the striatum, where they terminate in part in relation with the caudate nucleus. The connections of these groups with the cortex have been discussed by Cajal, d'Hollander, Ariëns Kappers and Gurdjian. Cajal described the mammillothalamic tract in

detail, and it has been generally recognized by students of the mammalian thalamus. Vogt (1909), d'Hollander and Gurdjian laid particular stress on the commissural fibers; Ariëns Kappers and particularly von Monakow emphasized the importance of the cortical connections.

The anterior dorsal, the most cephalic and the most dorsal of the group as its name implies, was described by Nissl, by Münzer and Wiener and by d'Hollander for the rabbit, and by Gurdjian for the rat. Cajal termed it "noyau angulaire" in mouse, and Friedemann and Vogt described it for the monkey under the name of the anterior accessory thalamic nucleus. It is the nucleus anterior *b* of Winkler and Potter, the rabbit and the cat, and the anterior *c* of von Monakow. Kölliker included it in the superior part of his intermediate nucleus, and Sachs and Ingvar applied to it the name of nuclei dorsales disseminati. Da Fano included it under the nucleus zonalis, and it is a part of the nucleus reuniens of Malone. It has been given various other names by workers on the diencephalon.

The second nucleus of the anterior group is the so-called nucleus anterior ventralis. It has been described under this name by Münzer and Wiener and d'Hollander for the rabbit, and by Gurdjian for the rat. It is the nucleus anterior *a* of von Monakow and Winkler and Potter and the dorsal superior nucleus of Cajal. Vogt called it the principal anterior nucleus, and Friedemann the anterior nucleus. It, with the other two nuclear groups, was included by Kappers in his anterior nucleus. Nissl combined the anterior ventral and anterior medial under the term of anterior ventral nucleus, but split it into secondary divisions which do not correspond with those of other authors. Sachs combined nucleus anterior ventralis with nucleus anterior medialis and gave the name of nucleus dorsalis magnus to the group. A similar combination of nuclei was called nucleus commissuralis thalami pars dorsalis by Malone.

Nucleus anterior medialis, the third member of the group, is the nucleus anterior *b* of von Monakow, probably the nucleus anterior *a* (fig. 2) of da Fano, the dorsal inferior nucleus of Cajal, the nucleus anterior of Friedemann, and the nucleus anterior *c* of Winkler and Potter; it is the nucleus anterior medialis of Münzer and Wiener, d'Hollander and Gurdjian, and the medialen Nebenkern *c* of Kappers.

Medial Nuclei.—The medial nuclei, as a group, lie ventral and later posterior to the anterior nuclei just described. They are medial to the lateral nucleus, and medial and dorsomedial to the ventral nucleus. They are more or less distinctly separated from the ventricular wall by the so-called nuclei of the midline. To this medial group belong several distinct cell masses characterized by differences in cell type and fiber connections. Of these the most conspicuous to be considered is the nucleus medialis dorsalis, which occupies much of the medial portion of the thalamus, ventral and then caudal to the anterior group, lateral to the midline nuclei and medial to the internal medullary lamina. An inner large-celled part (Friedemann) can be differentiated from the remainder of the nucleus. Between it and the ventral medial nucleus in many forms is the lateral extension of the central nucleus, the paracentral nucleus. Vogt, Cajal and others established connections of this nucleus with the cortex and it is connected also with the striatum. It

is generally conceded that in lower mammals commissural fibers connect it with the homologous nucleus of the other side. According to Probst (1900), some lemnisci fibers appear to reach it. These are probably trigeminal fibers.

This nucleus is the medialis *a* of von Monakow and *b* of Winkler and Potter, the nucleus medialis of Sachs, the central gray nucleus of Kölliker and the posterior medial nucleus of Nissl. By certain observers it has been divided secondarily into three parts. Thus, in the monkey, Friedemann described the chief medial nucleus with a zonal and a medial large-celled portion. These correspond to the divisions given by Kappers who termed the large cell part the nucleus magnocellularis. Observers in general have recognized this group of nuclei.

Ventral to the chief medial nucleus is the nucleus submedius of Vogt and others, in part at least the nucleus medialis ventralis of certain workers. Associated with the more caudal part of the nucleus medialis dorsalis, or chief medial nucleus, is the nucleus parafascicularis (Cajal, Friedemann and others). The possible relations of this nucleus have been discussed under the account of the habenulopeduncular tract. It is said also to receive fibers from the internal capsule and to be connected with the tectum.

Another small nucleus to be reckoned with the medial gray is the nucleus parataenialis of d'Hollander, Gurdjian and others. This nucleus lies in general near the dorsomedial portion of the nucleus medialis dorsalis in the forms in which it has been described and intervenes in part between the latter nucleus and the midline group with which the parataenial nucleus pars ependymarius of Friedemann is sometimes classified. It receives thalamic radiations from the internal capsule and in lower mammals is connected with the homologous nucleus of the other side by commissural fibers.

The nucleus parataenialis of d'Hollander, Gurdjian and others is the nucleus medialis parataenialis of Vogt, and probably part of the nucleus reuniens of Malone. Cajal termed it the lateral part of the superior nucleus of the raphe.

Nuclei of the Midline.—In lower mammals, such as rodents and carnivors, internal to the paired medial nuclei there is a series of cell masses situated in the midline of the thalamus and for the most part unpaired. To this midline group the name of commissura media or nucleus reuniens has been frequently applied, but a detailed study of the area in rodents and carnivora, at least, and probably in many lower mammals, shows that the area is capable of subdivision into a number of distinct nuclear groups. In primates these midline nuclei have become relatively inconspicuous, and in fact as true median structures have disappeared in man. Yet traces of them remain in the periventricular regions of the dorsal thalamus of the human being.

These nuclei of the midline have two primary functions: they are concerned in interrelating the various nuclei of one side with their homologous nuclei of the other side by means of interstitial nuclei with associated commissural fibers. Such connections involve not only the main nuclei of the internal division but also the centromedian nucleus and the ventral nucleus. A second important consideration with regard to these nuclei is their interconnection with the tuber cinereum region by way of the periventricular system of fibers, and their discharge through this system to the tectal and tegmental areas of the midbrain, from which centers pathways are open to somatic and visceral efferent centers by way of tectospinal paths and the dorsal longitudinal fasciculus of Schütze. The portions of the nuclei of the midline which persist in the higher mammals are probably those parts concerned with periventricular and possibly internal capsule connections, while the portions which disappear are those that are more or less exclusively commissural. The periventricular gray, then, in dorsal as well as ventral and subthalamic regions falls in part within the primitive discharge path to efferent centers. It receives visceral impulses from the tuber cinereum region and correlates these with impulses received from somatic centers of the dorsal thalamus and with gustatory. It connects with the dorsal medial nucleus of the thalamus and carries to that center impulses from the visceral areas of tuber cinereum. Internal capsule fibers have been traced to certain nuclei of the area but the direction of conduction is as yet unknown.

The following is a brief summary of certain of the more important midline groups found in subprimate forms: Beginning at the dorsal side of the diencephalon at a level passing through the cephalic part of the anterior nuclei, a nuclear mass is found in the midline which extends caudad throughout practically the whole extent of the diencephalon. This is the nucleus parataenialis, pars subependymarius of Friedemann, a part of the nuclei of the midline of Münzer and Wiener, and Nissl, and the nucleus paramedianus of Malone. It includes the paraependymal nucleus described for the cat by Winkler and Potter. It is the dorsal part of the nucleus reuniens of d'Hollander and the nucleus paraventricularis anterior and posterior of Gurdjian. In a plane passing through the anterior end of the medial habenular nucleus in the rat, Gurdjian found the commissural nuclei connecting the anterior dorsal and anterior medial thalamic nucleus. These lie just ventral to the nucleus paraventricularis anterior. Ventral to these commissural nuclei is the nucleus rhomboidalis, and below that the nucleus reuniens; further caudad the paired paraventricularis posterior replaces the anterior paraventricular group; the nucleus centralis occupies the former position of the nucleus rhomboidalis. After the disappearance of the nucleus reuniens, the nucleus commissuralis interventralis makes its appearance. The majority of these nuclear groups have been described in other mammalian forms. Thus the nucleus rhomboidalis of Gurdjian is a part of the middle portion of the nucleus reuniens of d'Hollander, a part of the nucleus of the midline of Münzer and Wiener, and is included in the commissura media of Sachs. According to Cajal, this nucleus receives corticothalamic and thalamocortical fibers. The nucleus reuniens of

Gurdjian is the ventral arcuate nucleus of Münzer and Wiener, is a part of the nucleus reuniens of d'Hollander, and receives periventricular and inferior thalamic radiations. Commissural nuclei between the various thalamic centers have been described by d'Hollander and Cajal.

Centromedian Nucleus.—In its position and general relations in certain mammals, the centromedian nucleus appears to belong to the medial group; in its fiber connections and consequent functional significance, at least in higher mammals, it is more directly related to the ventral group of thalamic nuclei. Its inclusion in the latter group permits of certain generalizations which are of value in the present discussion, and consequently for convenience we have considered it with the divisions of the ventral nucleus. It is of significance that difference in statements regarding the functions of the medial nucleus can frequently be reconciled when the inclusion or exclusion of this nucleus within the medial division is taken into account. Sachs and others have regarded this nucleus as related particularly to the lateral division of the thalamus. Many comparative neurologists, as von Monakow (*med. b*), Winkler and Potter have placed it with the medial group. Frequently there has been an unfortunate confusion of this nucleus with the cells in the internal medullary lamina. Vogt, Friedemann and others have identified a centromedian nucleus. This nucleus receives thalamic radiations from the internal capsule, the impulses apparently passing in both directions. According to some, it receives the medial part of the medial lemniscus, and Foix and Nicolesco believe that it receives secondary ascending fibers from trigeminal centers, that is, trigeminal lemniscus.

Ventral Nucleus.—In lower mammals the ventral nucleus consists of a round or oval mass of cells, resembling the nucleus rotundus of reptiles and birds, with which, in agreement with Ingvar and others, we believe it should be homologized. This oval mass is secondarily differentiable into two portions in the rabbit (d'Hollander) and in the rat (Gurdjian). In carnivors, the nucleus ventralis has lost its rotund form and can be divided into at least three distinct nuclear masses (Winkler and Potter, 1914). In monkey, Friedemann divided the area into caudal, medial and oral parts. A portion of his caudal and all of his medial division are comparable to the "noyau sensitif" of Cajal. This medial division alone is probably the semilunar nucleus of Dejerine, the arcuate nucleus of Kölliker and is within ventralis *b* of von Monakow. The oral portion of the nucleus is probably the same as the anterior semilunar nucleus of Cajal. In higher mammals the ventral nucleus occupies a considerable portion of the thalamus. It is situated between the lateral and centromedial nuclei, on the one hand, and the zona incerta, on the other. Cephalad to the level of the centromedial nucleus it lies in relation with the medial nucleus. Anteriorly it is bordered on

its lateral side by the reticular zone, but further caudad it lies ventrolaterally in relation with the zona incerta. It is to be regarded as one of the most important nuclei of the thalamus, for here terminate the major portion of the great ascending sensory systems, and from the nucleus arise the great majority of the projection fibers to the postcentral areas of the cerebral cortex.

Because of their great significance with reference to the function of the thalamus, these secondary ascending pathways have been diagrammed to show their relations and relative position; the following account should be read in connection with the diagram:

Painful impulses from the body pass to the spinal ganglia by way of unmedullated components of the peripheral nerves. The cells of origin of the fibers lie in the dorsal root ganglia, and their neuraxes, which are likewise unmedullated or only faintly medullated, enter the cord, reach a position at the tip of the dorsal horn and become components of Lissauer's tract. Individual neuraxes bifurcate and ascend and descend for not more than two segments. They terminate around cells of the substantia gelatinosa of Rolando. For the details of this termination and for an account of these fibers in general the work of Ranson (1913, 1914, 1915) should be consulted. The neuraxes of cells in the dorsal horn region of the cord carry these impulses across the midline to the ventrolateral part of the cord where, with others of their kind, they form the lateral spinothalamic tract. This tract occupies relatively a superficial position in its course through the cord, and retains this lateral position throughout much of its path. In the upper part of the pons region the lateral migration of the medial lemniscus brings the lateral spinothalamic path into close relation with the other lemnisci systems, and it runs forward as the most lateral component of the medial lemniscus to the more lateral parts of the ventral nucleus of the thalamus and to the centromedian nucleus of Luys. The main lateral spinothalamic tract is accompanied throughout its course by short fibers, contralateral and homolateral in type, which form a chain of neurons for the conveyance of the impulses to higher centers.

Tactile impulses are brought to the central nervous system over heavily medullated dendrites, the cells of origin of which are within the spinal ganglia. The neuraxes of such cells enter the cord with the medial division of the spinal nerves and bifurcate into long ascending and short descending branches. These branches give off collaterals at all levels of the cord through which they pass and these collaterals terminate in relation to dorsal horn gray. From this gray neuraxes of neurons of the second order, decussate in the anterior white commissure of the cord and run forward toward the higher centers as the ventral spinothalamic tract. In many cases the long ascending neuraxis of the primary neuron passes out of the cord to the nucleus gracilis or more frequently nucleus cuneatus of the medulla. The ventral spinothalamic tract has a ventral position throughout its course in the cord. Its position in the medulla is still a matter of dispute. According to Dejerine, whose results are shown in the accompanying diagram, the ventral spinothalamic tract comes into relation with the medial lemniscus within the medulla and runs forward with this fiber bundle. In the midbrain region, the ventral spinothalamic path lies medial to the lateral spinothalamic tract as they become incorporated within the general lemniscus system.

Proprioceptive impulses are brought forward from the body by way of the ascending fibers of fasciculus gracilis and cuneatus. These fibers synapse in the medullar nuclei of the fasciculi and then secondary neurons carry the impulse

by way of internal arcuates and the sensory decussation to the medial lemniscus of the opposite side. The work of Allan indicates that secondary visceral fibers from the gustatory centers, and the cephalic half of the general visceral centers of the medulla likewise cross the midline and run forward with these proprioceptive fibers as components of the medial lemniscus. From the spinal and chief sensory nuclei of the trigeminus, secondary fibers cross the midline and take up a position adjacent to the other lemnisci bundles. These fibers from the trigeminal centers are termed the ventral secondary ascending trigeminal tract and carry probably impulses of pain, temperature and general tactile sensibility. Another path forward from the chief sensory nucleus of the trigeminal nerve, phylogenetically younger and probably forming the pathway where tactile discrimination is involved, is the dorsal secondary ascending path of the trigeminal nerve, which retains its more dorsal position and runs for most of its course independently of the lemnisci bundles. From the preceding account and by consultation of figure 5, it is evident that the great ascending systems to the thalamus converge as they approach that area to form a great bundle of ascending fibers. Yet it is believed that they retain in the bundle their original position so that from outside toward the midline, the paths are successively lateral spinothalamic, ventral spinothalamic (ventral secondary trigeminal in close association) fibers and then gustatory and proprioceptive fibers from the medial lemniscus proper, with the dorsal secondary trigeminal tract lying outside the main mass. In their distribution within the thalamus, the evidence suggests that the more medial portions of the bundle reach the more medial parts of the ventral nucleus while the more lateral parts distribute to more lateral regions of this nuclear mass (Wallenberg, 1900). It is known from the work of Vogt that the more medial part of the lemniscus reaches the medial and lateral caudal regions of the ventral nucleus of the thalamus, and that the trigeminal fibers and fibers from the dentate nucleus of the cerebellum and the red nucleus reach the intermediate lateral portions of the ventral nucleus. Into the lateral parts of the nucleus pass likewise the spinothalamic tracts. The dentothalamic and rubrothalamic fibers bring forward by way of the cerebellum proprioceptive impulses including those from the vestibular complex. The lateral spinothalamic and the trigeminal components pass likewise to the centromedian nucleus, and fibers of the median lemniscus of character as yet unknown reach the posterior nucleus of the thalamus. Medial lemnisci fibers also distribute to the posterior nucleus and according to Probst (1900), to some extent, to the medial nucleus. Von Monakow regarded the lateral nucleus as the thalamic center connected with the lower limb centers of the precentral and postcentral gyri. This would imply lemnisci connections with the lateral nucleus. Flechsig carried projection fibers from the anterior and posterior parts of the ventrolateral nuclei (ventral nucleus region) to the lower third and upper third of the postcentral convolutions (the posterior to upper third of central). The middle third of the central convolutions received fibers from the region of the arcuate and centromedian nuclei.

The account given indicates clearly that general sensibility, tactile, temperature and pain, from head and body are brought to the ventral nucleus of the thalamus by way of the ventral ascending trigeminal tract and the lateral and ventral spinothalamic systems. Of these, the trigeminal components are known to reach lateral intermediate parts of the thalamus, and the spinothalamic components are believed to reach its lateral portion. Proprioceptive impulses from vestibular and

other bulbar and spinal centers distribute by way of the superior cerebellar peduncles to the areas reached by the secondary trigeminal fibers. Proprioceptive impulses, exteroceptive for tactile discrimination (and probably gustatory fibers) also reach the ventral nucleus of the thalamus. Thus, this nucleus is above all the thalamic center of termination for exteroceptive, proprioceptive and possibly gustatory impulses. Here they are relayed to motor centers of the ventral thalamus by way of connections with the zona incerta and possibly other ventral nuclei, and thus make provision for thalamic reflexes. The ventral nucleus of the thalamus is connected with the striatal areas by thalamostriatal fibers, particularly by inferior thalamic radiations (ansa peduncularis), and it has connections with the other thalamic nuclei by way of internuclear fibers and so provides for interthalamic correlation. It sends fibers through the posterior limb of the internal capsule for the projection of the various sensory impulses on the cerebral cortex.

Lateral nucleus.—The differentiation of the lateral nucleus is in direct relation to the position of the animal in the mammalian scale of development. Thus, in the lower mammals it is a single nuclear mass with possibly a slightly differentiated external posterior portion, which receives optic fibers, has connections with the lateral geniculate and so is looking forward to the development of the pulvinar. In the cat, Winkler and Potter (1914) have demonstrated the presence of two lateral nuclei (nuclei lateralis *a* and *b*) which are here termed nucleus lateralis anterior and nucleus lateralis posterior. Vogt described three and Friedemann three (two major and a minor) nuclear masses with subdivisions in the lateral nucleus of monkey, and von Monakow identified an anterodorsal and a caudoventral portion in the lateral thalamic nucleus in man.

The nucleus lateralis is interconnected with the ventral and medial nuclei of the thalamus. Various observers have traced fibers of the internal capsule to it, but there is uncertainty in regard to direction of the impulse. Von Monakow regarded this nucleus as connected with frontal, precentral, postcentral and parietal areas. In our judgment both ventral and lateral nuclei of the thalamus increase in size and nuclear differentiation with the development and differentiation of the cortical centers. The ventral nucleus differentiates with the projection centers, the presence within it of specific nuclei forecasting and postulating the appearance of the localization within these cortical areas, while the lateral nucleus develops hand in hand with the nonprojection or essentially association cortical areas, perhaps also with projection cortex.

Along the border of the lateral and ventral nuclei of the thalamus, intercalated in the course of internal capsule fibers, are found scattered masses of gray matter which constitute the reticular nuclei.

Pulvinar.—The pulvinar is present as a distinct nuclear group only in higher mammals. It has been described for the cat (Winkler and Potter, 1914), and for the monkey (Friedemann and Vogt). The latter observers have indicated the presence of many subdivisons within this nuclear mass, but since such subdivisions are based on cyto-architectonic and myelo-architectonic structure of the nucleus rather than on specific fiber connections, they will not be discussed further here. Most observers are agreed that the pulvinar receives direct optic fibers and that it is connected with the lateral geniculate nucleus and the superior colliculus. Connections between the pulvinar and the area striata of the cortex have been described repeatedly, but there appears still to be some question with regard to the direction of the conduction of impulses.

Lateral Geniculate Body.—The lateral geniculate bodies exhibit two nuclei, a dorsal and a ventral one, in mammals through the lower primates (Woollard and others). A distinct ventral nucleus has not been demonstrated in higher primates, including man. Of these two nuclei, the ventral is phylogenetically the older. As far down as fishes, collaterals of the optic tract terminate in the diencephalon, and in amphibians an optic thalamic nucleus is present. This becomes more highly differentiated in reptiles and is the anlage of the ventral nucleus of the lateral geniculate body of higher forms. In all submammalian types the lateral geniculate body is preeminently a dependency of the tectum, with which it is connected by numerous tracts which conduct impulses in both directions. Passing caudad from the lateral geniculate body in *Varanus* (Beccari), and in the alligator (Huber and Crosby), is a descending tract to the motor centers, the fasciculus geniculatus descendens. The presence of numerous tectogeniculate fibers and of this descending tract indicates that one important function of the primitive geniculate body is to provide a mechanism for the correlation of optic impulses with those from tectal centers (which include in these forms auditory, tactile and general sensibility as well as optic), and provision of a means of discharge to motor centers. In *Sphenedon* (Cairney) there is the beginning of a dorsal nucleus of the lateral geniculate body. Even in lower mammals the latter nucleus has shown relative increase, while the ventral nucleus, with a decrease in the dominance of the tectum in mammalian forms, is relatively smaller and shows relatively less differentiation. The relations in such a mammalian form are indicated in the subdiagram of figure 7. Here, incoming optic fibers are distributed to the primitive pulvinar and to the ventral and dorsal nuclei of the lateral geniculate body, the dorsal nucleus being connected chiefly with the cerebral cortex while the ventral nucleus is interconnected with the tectum and gives rise to the descending fasciculus. Woollard has shown, in the study of a series of closely related higher mammals including primates, that there exists a progressive disappear-

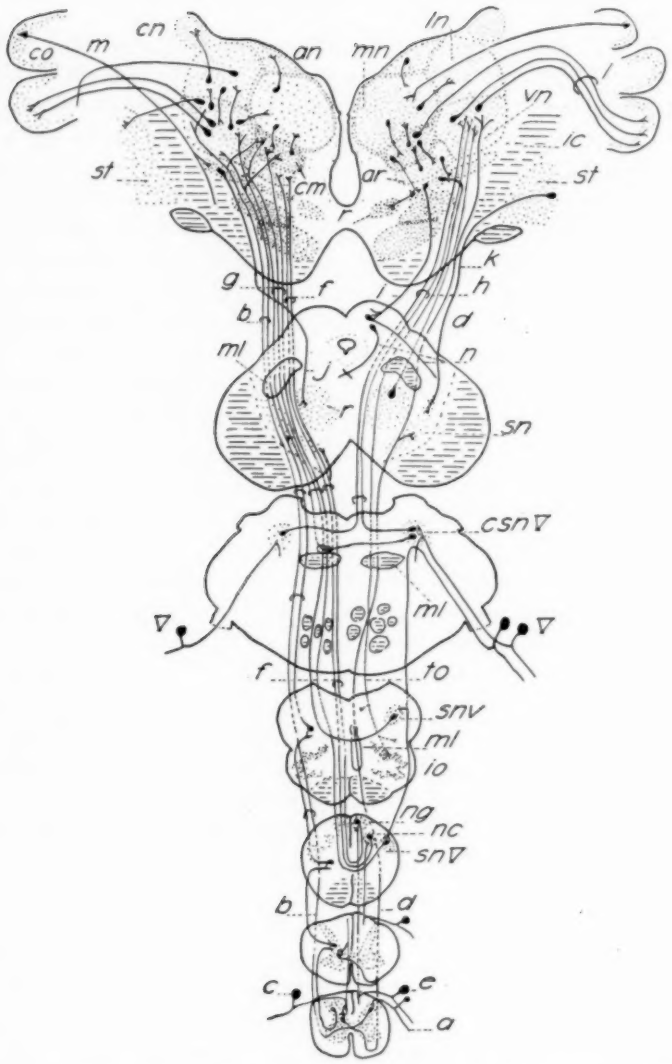

FIG 5.—Diagram illustrating the relations of the lemnisci system: *a*, neuron carrying pain or temperature; *an*, anterior thalamic nucleus; *ar*, arcuate nucleus; *b*, lateral spinothalamic tract; *c*, neuron carrying tactile impulses; *cm*, centromedian nucleus of Luys; *cn*, caudate nucleus; *co*, cortex; *csnV*, chief sensory nucleus of the fifth nerve; *d*, ventral spinothalamic tract; *e*, proprioceptive neuron; *f*, proprioceptive portion of medial lemniscus; *g*, ventral trigeminal projection tract; *h*, dorsal trigeminal projection tract; *i*, incertotectal tract; *ic*, internal capsule; *io*, inferior olivary nucleus; *j*, incertorubral tract; *k*, strionigral tract; *l*, thalamocortical tract to postcentral gyrus; *ln*, lateral thalamic nucleus; *m*, corticospinal tract from precentral gyrus; *ml*, medial lemniscus; *mn*, medial thalamic nucleus; *n*, crossed and uncrossed tectospinal tracts; *nc*, nucleus cuneatus; *ng*, nucleus gracilis; *r*, red nucleus; *sn*, substantia nigra; *snV*, spinal nucleus of the fifth nerve; *st*, striatum; *to*, thalamo-olivary tract; *vn*, ventral thalamic nucleus.

ance of that part of the lateral geniculate body which is related to the tectal centers. As previously stated, this nucleus has not been demonstrated in man. The dorsal part of the lateral geniculate nucleus has increased progressively in the mammalian phylum, so that in higher mammals, such as *Carnivora*, it has acquired an elaborate laminated structure, the cyto-architecture of which has been described by several recent observers (Minkowski 1913 and 1919, and others), and recently has been modeled and described in detail by Thuma for the cat. For further details, reference should be made to the original contributions. Similarly, the details of the projection of the quadrants of the retina on the lateral geniculate nucleus and the details of its projection on the cortical area must be obtained from the literature. There have been so many recent reviews of the literature dealing with this subject that further discussion here is deemed unnecessary. Reference is here made to the work of Minkowski, Brouwer, Brouwer and Zeeman, Henschen, Putnam. From the foregoing statements it will be seen that the lateral geniculate body receives optic fibers, that it is interconnected with the tectum and with the pulvinar, and that it sends fibers to the area striata of the cortex. Whether or not a descending geniculate fasciculus is present in higher mammals is uncertain.

The Optic Tract (fig. 6).—From the rod and cone layer of the retina, nervous impulses are passed to the bipolar cells and from there to the ganglion cells of the retinal layer. The neuraxes of these ganglion cells course to the brain as the optic nerve, those fibers from the nasal side of the retina decussating in the optic chiasma and those from the temporal portion passing back on the same side. Beyond the chiasma these crossed and uncrossed fibers form the optic tract which distributes to the superior colliculus, to the lateral geniculate and to the pulvinar; the fibers (mainly crossed) to the superior colliculus are concerned with light reflexes and the impulse, after a synapse in this region, is distributed either by the radiations of Meynert to the Edinger-Westphal nucleus of the third or by the tectospinal path and presumably the medial one to the intermediolateral column in the first four segments of the thoracic cord. From the Edinger-Westphal nucleus, impulses are carried over the oculomotor nerve to the ciliary ganglion, where these preganglionic fibers synapse with the cell bodies of postganglionic neurons which distribute to the ciliary muscle and to the circular fibers of the iris. They provide thus for accommodation and are the sphincter fibers of the pupil. The preganglionic fibers from the thoracic cord leave the cord by way of the spinal nerves, pass out to the chain ganglia and forward along the sympathetic chain to the superior cervical sympathetic ganglion where they synapse. Postganglionic fibers run forward from this ganglion to the dilator apparatus of the eye and so permit an increase in the size of the pupil. The optic fibers which terminated in the lateral geniculate body are in synaptic connection with neurons, the neuraxes of which pass to the superior colliculus, to the pulvinar or to the area striata of the cerebral cortex. Those to the tectum run in the peduncle of the superior colliculus. This peduncle carries also fibers from the pulvinar and from the lateral geniculate and for part of their course fibers directly from the area striata of the cerebral cortex to the superior colliculus. Corticothalamic fibers likewise pass to the pulvinar. There is disagreement as to the presence of thalamocortical fibers from this nucleus to the cerebral cortex. Visual reflexes are mediated by way of the thalamus, at least

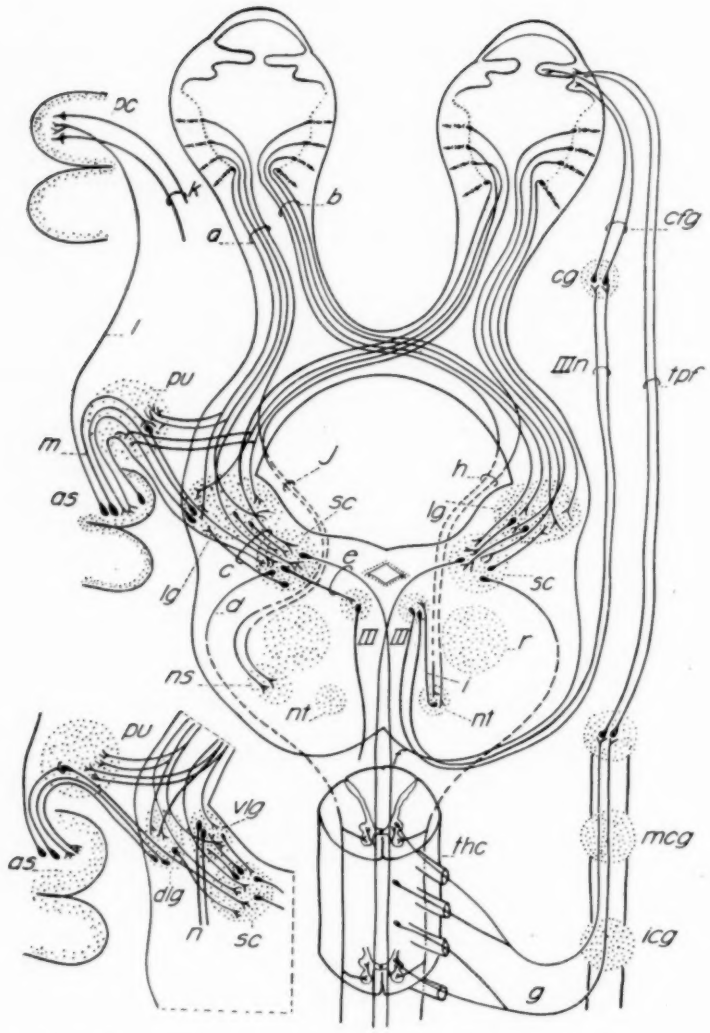

FIG. 6.—Optic connections: *a*, uncrossed or temporal optic fibers; *as*, area striata; *b*, crossed or nasal optic fibers; *c*, brachium or peduncle of the superior colliculus; *cg*, ciliary ganglion; *cfg*, craniosacral postganglionic fibers; *d*, lateral tectospinal path; *e*, Meynert's radiation; *f*, medial tectospinal path; *g*, thoracicolumbar preganglionic fibers; *h*, tractus pedunculus transversus (posterior accessory optic tract of Bochenek); *i*, connections between the nucleus of the tractus pedunculus transversus and the nucleus of the third nerve; *icg*, inferior cervical sympathetic ganglion; *j*, anterior accessory optic tract of Bochenek; *k*, corticospinal tract; *l*, cortical association path; *lg*, lateral geniculate; *m*, corticopulvinar fibers; *mcg*, middle cervical sympathetic ganglion; *n*, fasciculus geniculatus descendens of Beccari; *ns*, nucleus subthalamicus; *nt*, nucleus of the tractus pedunculus transversus; *pc*, precentral cortex; *pu*, pulvinar; *r*, red nucleus; *sc*, superior colliculus; *scg*, superior cervical sympathetic ganglion; *thc*, thoracic spinal cord; *tpf*, thoracicolumbar postganglionic fibers; *vlg*, ventral nucleus of the lateral geniculate; *III*, efferent nucleus of the third nerve; *IIIn*, third nerve.

in the highest mammals, and disappear with destruction of the optic thalamic centers even if the superior colliculus and the tracts passing to and from it are intact. An efferent pathway, however, for visual reflexes may pass from the thalamus to the superior colliculus and then by way of the radiations of Meynert to the nuclei of the extrinsic muscles of the eye in the oculomotor, trochlear and abducens nerves, the latter two nuclei being connected with the nuclei of the oculomotor by means of the medial longitudinal fasciculus.

In addition to the optic tract fibers thus far described, there are two accessory optic tracts of Bochenek. The optic fibers in the anterior accessory tract, after a partial decussation in the optic chiasma, separate from the main optic bundles and run caudad in the depths of the thalamus to the subthalamic nucleus of Luys. The posterior accessory optic tract of Bochenek is better known as the tractus pedunculus transversus. This tract runs caudad along the ventral surface in relation to the cerebral peduncle and then turns dorsad to terminate in the nucleus of the tract, which is situated along the side of the peduncle at about the level of the interpeduncular nucleus and slightly dorsolateral to it. The nucleus of the tractus pedunculus transversus has a connection with the oculomotor nucleus. This account should be studied with figure 6 in mind.

The medial geniculate body has been divided into several nuclear groups, but homologies in the different forms are difficult to make by reason of the absence of details of fiber connections in many cases. Cajal divided the nuclear mass into a superior lobe, associated with Gudden's commissure and the peduncle of the inferior colliculus, and an inferior lobe, which received fibers of the lateral lemniscus. Both lobes gave rise to thalamocortical fibers. Associated with these nuclear masses was recognized an internal nucleus, consisting of large cells, which was in association with the nucleus of the lateral lemniscus. Three portions of the medial geniculate nucleus were figured by Winkler and Potter in their atlas on the cat. The diagram presented in figure 7 represents our conception of the auditory connections.

Auditory Connections—Figure 7.—The neurons of the first order for auditory impulses lie in the spiral, cochlear ganglion. Their neuraxes enter the medulla and synapse in the dorsal and ventral cochlear nuclei. From the dorsal cochlear nucleus fibers pass as stria medullaris acustici across the floor of the fourth ventricle to the midline, where they swing ventrolaterad to enter the lateral lemniscus of the same and opposite sides. From the cells of the ventral cochlear nucleus, neuraxes course mediad, cross the midline and enter the lateral lemniscus of the opposite side; on their way they give collateral and stem fibers to the superior olivary nuclei and the trapezoid nuclei of the two sides. These fibers, which constitute the trapezoid body, are joined by tertiary fibers from the trapezoid nuclei. Thus at about the middle of the pons, the lateral lemniscus is composed of crossed and uncrossed fibers arising from the neurons of the dorsal cochlear nucleus and the trapezoid nucleus, and fibers from the contralateral ventral cochlear nucleus. As the lateral lemniscus runs cephalad, certain of its fibers come into synaptic relation with scattered gray matter termed the nucleus of the lateral lemniscus. The lateral lemniscus terminates in the inferior colliculus of the midbrain, and the medial geniculate nucleus of the thalamus. From the inferior colliculus impulses are likewise carried to the medial geniculate by way of its peduncle. Acustico-optic or intertectal fibers connect the inferior with the

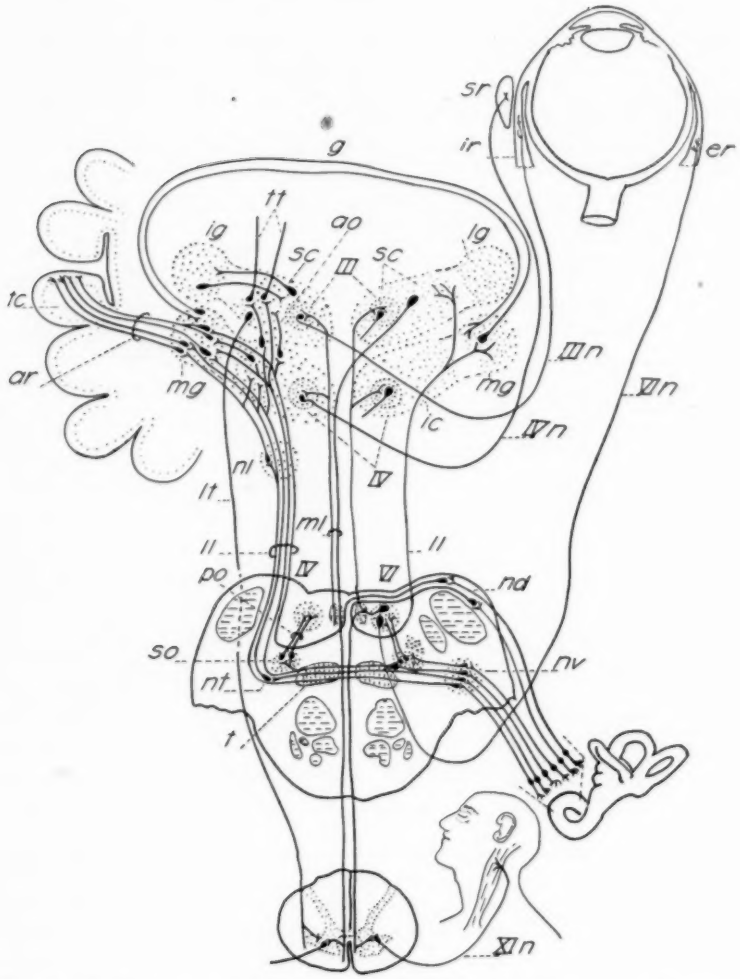

FIG. 7.—Auditory connections: *ao*, acustico-optic radiations; *ar*, auditory radiations; *er*, external rectus; *g*, Gudden's commissure; *ic*, inferior colliculus; *ir*, internal rectus; *lg*, lateral geniculate body; *lt*, lateral tectospinal path; *ll*, lateral lemniscus; *mg*, medial geniculate; *ml*, median longitudinal fasciculus; *nd*, dorsal cochlear nucleus; *nl*, nucleus of the lateral lemniscus; *nt*, nucleus of the trapezoid body; *nv*, ventral cochlear nucleus; *po*, superior olivary peduncle; *so*, superior olivary nucleus; *sc*, superior colliculus; *sr*, superior rectus; *t*, trapezoid body; *tc*, temporal cortex; *tt*, tectothalamic tract; *III*, nucleus of the third nerve; *IIIn*, oculomotor nerve; *IV*, nucleus of the fourth nerve; *IVn*, trochlear nerve; *VI*, nucleus of the sixth nerve; *VIn*, abducens nerve; *XIn*, spinal accessory nerve.

superior colliculus and thus make possible the transmission of auditory impulses from inferior to superior regions and then to motor centers of bulb and cord by way of tectobulbar and tectospinal paths. The peduncle of the superior olive, which connects with the motor nucleus of the sixth nerve, relays auditory impulses to this nucleus, whence they are distributed by way of the medial longitudinal fasciculus to the motor nuclei of the third and fourth nerves and to the spinal motor nucleus of the eleventh cranial nerve. Thus the provision is made for the reflex of turning the head and eyes in the direction of the sound. The auditory impulses reaching the medial geniculate by way of the lateral lemniscus and the peduncle of the medial geniculate, after relay in this thalamic center, are carried to the cortex by way of sublenticular auditory radiations to Heschl's convolution. These several paths here depicted are to be seen in figure 7.

A posterior thalamic nucleus has been described in various mammals, but the area so designated has not always received the same delimitation. Thus, the posterior nucleus of one author may include the pretectal nucleus, or part of the lateral nucleus, or even the pregniculate nucleus of another author. Since various mammalian forms have been considered and in most instances the fiber connections are unknown, it is extremely difficult and on the whole, unprofitable to attempt to make exact homologies at the present time. In mammals, the posterior thalamic nucleus lies at the caudal end of the diencephalon, extending back to the midbrain region. On the whole, its position is ventral and ventromedial to the lateral nucleus, and for the most part dorsomedial to the lateral geniculate body. It receives fibers from the medial lemmiscus and is connected with the tectum and the cortex.

In submammalian forms there is a well developed group of nuclei in the boundary region between diencephalon and tectum. With the reduction of the superior collicular portion of the tectum this pretectal gray is apparently reduced. In only a few forms, such as the rat (Gurdjian), has a definite pretectal nucleus been described; usually the area has been included under the posterior thalamic nucleus (d'Hollander). To what extent other portions of the posterior nucleus are to be regarded as derivatives of the primitive pretectal group is at present uncertain. When differentiable, this pretectal nucleus is connected with the tectum. It is our conviction that there is a distinct need of a more thorough understanding of tectothalamic and thalamotectal connections in mammals, particularly in view of their phylogenetic significance.

VENTRAL THALAMUS

The ventral thalamus, or the subthalamus, one of the major divisions of the diencephalon, in general lying ventral to the sulcus medius, is to be regarded particularly as a place of origin or synapse of efferent pathways. To this region are allocated the zona incerta, fields H of Forel, the entopeduncular nucleus, the nucleus subthalamicus and the cephalic prolongations of the substantia nigra and the nucleus ruber.

In addition to these, there are smaller nuclear groups of which no discussion will be attempted here.

Zona Incerta.—The zona incerta consists of scattered cells lying in the course of certain efferent fiber bundles from the internal capsule. It is situated in the dorsal part of the subthalamus, immeditaely ventral to the ventral thalamic nucleus, and is not sharply delimited from the surrounding area. This area probably receives collaterals from corticospinal and corticobulbar fibers, possibly also terminal fibers from the cortex. It is connected with the striatum through collaterals of fibers found in the ansa lenticularis; it is connected with the medial and ventral nuclei of the dorsal thalamus and probably with the contralateral homologous area through the fibers of Meynert's commissure (fig. 1). This nucleus probably contributes fibers to the descending motor pathways, and is connected with the tectum and tegmentum of the midbrain by way of incertotectal and incertotegmental paths. It is connected with the rostral end of the red nucleus and the subthalamic nucleus, and likely with other nuclei of the ventral thalamus. It probably gives rise to thalamobulbar and thalamo-olivary paths (in part), but there is need of confirmation for these last two connections. These connections for zona incerta and the remainder of ventral thalamus or subthalamus are based on personal observation and the accounts of other authors, among whom may be mentioned von Monakow, Dejerine, Cajal, Wilson, 1913-1914, Hunt, Tilney and Riley, Foix and Nicolesco and others.[1] Fields H_1 and H_2 of Forel consist of scattered gray in the course of distinct bundles (portions of the efferent systems from the corpus striatum) which were described by this author and are known as the radiations of Forel. Of these radiations H_1 is the thalamic fasciculus and H_2 the lenticular fasciculus of Forel.

Entopeduncular Nucleus.—The term entopeduncular nucleus is applied to a small group of relatively large cells found in conjunction with the ansa lenticularis; it constitutes a region of synapse for efferent pathways.

The Subthalamic Nucleus.—The subthalamic nucleus, or hypothalamic nucleus or the corpus Luysi, an approximately oval nuclear mass in higher mammals, is situated in close relation to the rostral end of the substantia nigra. It is connected with its fellow of the opposite side through commissural fibers found in the supramammillary com-

1. In figure 8, we show bundles passing directly from the caudate nucleus and the putamen, as well as from the globus pallidus, into the ventral division of the ansa lenticularis; this follows the recent account of Foix and Nicolesco (1925). It is not entirely in agreement with the statement of Wilson, 1913-1914 (based on monkey), that the main striofugal and striopetal paths come into relation only with the globus pallidus and are not directly related with the putamen and globus pallidus.

missure (fig. 8) and with the substantia nigra and the zona incerta. It is connected with the striatum (caudate nucleus and putamen and globus pallidus) by way of the striosubthalamic fasciculus. The subthalamic nucleus receives also the posterior accessory optic tract of Bochenek.

Substantia Nigra.—The substantia nigra, constituting a mass of gray matter lying in definite relation to the cerebral peduncle and extending forward from the midbrain region into the ventral thalamus, is composed of cells having a definite pigmentation, which apparently increases definitely with the advent of puberty. This nuclear mass, in addition to other internuclear connections with subthalamic nuclear masses, is connected with the globus pallidus by way of the medial and ventral divisions of the ansa lenticularis of von Monakow, and is believed to receive collaterals from corticobulbar and corticospinal fibers and also has tectal and tegmental connections.

Nucleus Ruber.—The nucleus ruber consists of a small and a large celled nuclear portion, as the work of von Monakow and others has indicated and our own material confirms. The general appearance, the position and relations of this nucleus are so generally known that a detailed description may with propriety be here omitted. Afferent impulses reach this nucleus from the cerebral cortex by way of the corticorubral path, from the striatum by way of the dorsal and ventral divisions of the ansa lenticularis of von Monakow, from the zona incerta and probably other subthalamic centers by way of incertorubral and other internuclear connections, and from the dentate nucleus of the cerebellum through crossed fibers of the superior cerebellar peduncles. The main efferent pathways are the rubrothalamic, the rubroreticular or rubrobulbar and rubrospinal of von Monakow. The rubrothalamic, with the secondary ascending trigeminal fibers, form the fasciculus prelemniscale of Vogt, which, according to this author, distributes to the caudal portion of the ventral nucleus of the dorsal thalamus (Va_1 of Vogt and Friedemann). The rubrobulbar and rubrospinal paths pass to motor centers of the bulb and spinal cord. The main afferent and efferent pathways, as they relate to the subthalamus, are delimited primarily in figure 8. Other figures of the series, particularly figure 5, show certain further connections. Attention is called especially to the connections of the dorsal, medial, and ventral portions of the ansa lenticularis of von Monakow.

COMMENT ON THE DORSAL AND VENTRAL THALAMUS

The general functions of the dorsal and ventral thalamus have been suggested in the introductory lines followed by a discussion of the nuclear pattern in its relation to fiber connections. An attempt may now be made to state, at least in general terms, the relations existing between structure and function.

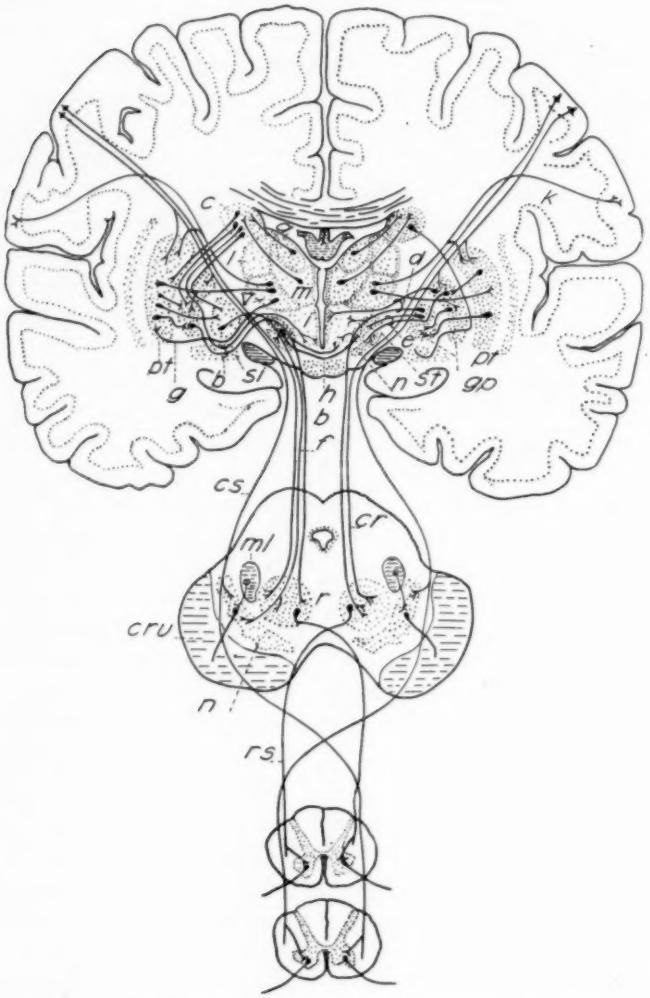

FIG. 8.—Thalamostriatal and striothalamic conduction pathways: *a*, anterior thalamic nucleus; *b*, ansa lenticularis; *c*, caudate nucleus; *cr*, corticorubral tract; *cru*, crura; *cs*, corticospinal tract; *d*, lenticular fasciculus of Forel; *e* and *f*, fasciculus striosubthalamicus; *g*, part of ventral thalamic peduncle; *gp*, globus pallidus; *h*, commissural connections of nucleus subthalamicus by way of supramammillary commissure; *i*, zona incerta and fields of Forel; *k*, thalamocortical radiations to postcentral gyrus; *l*, lateral thalamic nucleus; *m*, median thalamic nucleus; *ml*, median lemniscus; *n*, substantia nigra; *pt*, putamen; *r*, red nucleus; *rs*, rubrospinal tract; *si*, substantia innominata; *st*, nucleus subthalamicus; *v*, ventral thalamic nucleus.

The medial division of the thalamus has been shown to consist of an anterior, medial and midline group of nuclei. The anterior group receives olfactovisceral impulses from the hypothalamus; the medial group receives tactile, pain and temperature impulses, but for the most part indirectly by way of internuclear fibers from the ventral thalamic nucleus. Olfactovisceral impulses, by way of the periventricular system from the tuber cinereum, reach certain nuclei of the midline and so directly or indirectly the medial nucleus. Interrelation of the medial nucleus with the anterior nucleus brings to it also olfactovisceral impulses. Thus the medial nucleus becomes a center of correlation for exteroceptive (general sensibility, pain and temperature) and interoceptive (olfactory, gustatory and possibly general visceral sensations) impulses, and to what extent proprioceptive impulses reach it is uncertain. Within itself the medial nucleus and its associated nuclei present no pattern, nor do they have the specific type of connections, which would suggest a definite localization of impulses within them; on the contrary, they indicate such interrelation and correlation of impulses as would provide the anatomic basis for general affective tone. A further confirmation of the lack of localization within the medial nucleus and the medial division in general is to be found in the fact that it connects with the frontal lobe, regarded as an association rather than a projection center. Tilney and Riley regard the latter connection as providing the anatomic basis for personality and behavior. It is certain that impulses reaching this area from the medial nucleus will frequently represent the integration of a variety of bodily stimuli, and that such impulses discharging through association fibers to afferent and particularly to efferent centers will modify to a considerable degree the type of response to a given stimulation. However, just as the stimuli of the medial division modify the responses from the cortex, so the cortical centers modify and direct and in certain cases inhibit responses from the medial division. In part this is effected through corticothalamic fibers which pass directly to these medial nuclei, and in part it is accomplished through the action of efferent cortical paths on the efferent centers of the subthalamus, bulb and spinal cord through which these nuclei may discharge.

For purposes of discussion, the lateral division of the dorsal thalamus may be divided into two groups. To one of these groups may be allocated those centers which are primarily nuclei of termination for the ascending secondary sensory paths, such as the medial and lateral lemnisci and the optic tract. Such centers are the centromedian nucleus, the ventral nucleus, the posterior nucleus, the pulvinar and the medial and lateral geniculate nuclei. These nuclei develop hand in hand with the development of the projection centers of the cerebral cortex, and the distinctness with which the various groups of impulses are delimited

within them is reflected in the specificity of the cortical projection centers. Thus the optic and auditory cortical centers can be distinguished sharply from other sensory projection centers, just as their thalamic nuclei are clearly definable from other thalamic areas, while the pain, temperature and tactile impulses, which are not so definitely localized with respect to each other in the diencephalon, are discharged into a single, general cortical area. The nuclear groups within the ventral nucleus are looking forward to such a localization, for cortical localization must always have its basis clearly defined in the dorsal part of the diencephalon. The ventral nucleus is phylogenetically old. The nucleus rotundus of lower forms appears to us to be its precursor, as Ingvar and others have also thought, and not the forerunner of the medial nucleus, as is sometimes believed. It is significant that in lower mammals it retains its primitive form, and that it is only in higher mammals and in primates, in which the pattern of cortical localization specific for these forms is established, that the ventral nucleus attains its greatest differentiation. This is further evidenced in the relation existing between the development of the dorsal nucleus of the lateral geniculate nucleus and the elaboration of the cortical optic centers. For while the ventral part of the lateral geniculate nucleus is represented in nearly all submammalian forms from fishes on, the dorsal nucleus is phylogenetically of much later development, being only meagerly represented in reptiles, not attaining its full nuclear pattern until higher mammalian forms are reached; consequently, the number of projection fibers to the forebrain from the optic thalamic centers is relatively small in most submammalian forms and increases *pari passu* with the increase of the dorsal geniculate nucleus.

The centromedian nucleus has a significant location, situated as it is between the ventral and the medial nuclei of the thalamus. The majority of workers on lower mammalian forms have placed it with the medial group. Certain of the observers who have studied higher forms have delegated it to the lateral division of the thalamus. Just as it is intermediate in position, so it is intermediate in its connections. It is in close synaptic relation with the nuclei of the midline and the medial nucleus, and thus presents certain of the functional characteristics of the medial group. It resembles the ventral nucleus of the lateral division in being a major region of termination of secondary ascending paths. It is of particular interest to note that of these ascending paths, those carrying pain (lateral spinothalamic and trigeminal fibers) and possibly general sensibility, synapse in part in the centromedian nucleus. (Some few lemnisci fibers are said to reach the medial nucleus [Probst 1900]). May we hypothecate that this center will be involved in thalamic consciousness of pain? There is within the lateral division of the dorsal thalamus a group of nuclei not concerned primarily with the reception of ascending sensory impulses and their

transmission to cortical projection centers. Of this group the lateral nucleus is the most typical representative. Beginning apparently as a single nuclear group in lower mammals, it increases in size and in differentiation with the advance in the mammalian scale and reaches its highest differentiation in primates. Inadequate knowledge of the thalamic relations of the lemnisci makes it uncertain whether they are main determining factors in its development, while its connection with association centers of the cortex postulates that it develops hand in hand with the development of the latter cortical areas. Thus in any mammalian form, the ventral nucleus develops and differentiates with the projection centers, while the lateral nucleus probably differentiates with the differentiation of the association centers. What other factors may have a rôle to play in its development we are not at present prepared to say. However, it should be emphasized that the lateral division of the thalamus has portions which are phylogenetically so old that if a division into paleothalamic and neothalamic centers is to be made, it cannot be made on the basis that the medial thalamus is phylogenetically older than the lateral thalamus, for both medial and lateral divisions contain paleothalamic and neothalamic constituents.

The account given indicates that the dorsal thalamus is on the afferent side of the arc. Quite as definitely the ventral thalamus or subthalamus is concerned in the transmission of efferent impulses. It receives impulses from four major areas, namely, the cortex, the striatum, the dorsal thalamus and to some extent the hypothalamus. The cortical connections are by way of collaterals from corticobulbar and corticospinal and probably corticorubral paths, and through stem fibers synapsing in the zona incerta and adjacent gray, in the substantia nigra and in the red nucleus. The major striatal connections to the subthalamic area are by way of the dorsal, medial and ventral divisions of the ansa lenticularis (von Monakow). The most dorsal of these, after passing directly through the posterior limb of the internal capsule, supplies the fields of Forel, the periventricular gray, and sends fibers to the red nucleus. The medial division distributes to the subthalamic, the red nuclei and the substantia nigra. This medial division likewise passes through the internal capsule, but the ventral division is sublenticular in its course, being a part of the ansa peduncularis. This ventral division terminates in the red nucleus and in the field of Forel of the same and the opposite side, after decussation in the supramammillary commissure. In view of the significant work of Ramsay Hunt and others on the importance of the striatum in the control of automatic associated movements, the striatal paths here enumerated are deserving of special consideration. Knowledge of them is owing to the painstaking work of Forel, Dejerine, von Monakow and others. It is evident that such subthalamic paths as those described, from cortex and striatum, indirectly afford pathways of discharge for dorsal thalamic centers.

Reference should be made to figure 8 in which the connections of the dorsal thalamus with the subthalamic centers are indicated. The dorsal thalamus and the hypothalamus as well, through their connections with zona incerta, may discharge directly to motor centers of the bulb, through thalamobulbar and thalamo-olivary paths, and to the tectal and tegmental centers, including red nucleus, by means of incertotectal and incertotegmental paths. This connection makes possible the simpler thalamic reflexes. It must be evident from this account that the thalamus is much more than a gateway to the cortex; it is an exceedingly important reflex center and a center involved in affective tone.

One of the aims in this presentation has been to indicate the gaps in our knowledge of thalamic connections, and particularly of those concerned with the mediation of visceral sensibility. It will be noted that no definite paths have been traced from the visceral centers of the spinal cord and the lower part of the medulla to thalamic centers. Suggestions of possible paths for these impulses are found scattered through the literature, but these are sadly in need of further confirmation. It is possible that the general visceral afferent impulses are carried to diencephalic centers by nonmedullated fibers, or even more probably by a chain of neurons similar to those associated with the lateral spinothalamic path (fig. 5). Further analysis of the periventricular fiber system, particularly in its relation to the periventricular gray in the diencephalon and mesencephalon and its relation to the tegmental nuclei and other efferent centers, would be of great value for an understanding of the discharge paths of the visceral areas of the diencephalon. This system undoubtedly involves, in part, chains of neurons rather than uninterrupted neuron paths.

It is to be remembered that the primitive conducting pathways of the nervous system are in the form of a series of neurons, comparable to links in a chain. With the need of greater specificity and speed of conduction, these neuron chains are replaced during phylogeny and sometimes during ontogeny, as in amphibians (Herrick and Coghill), by longer conducting elements which may carry impulses without synapse for considerable distances. The main conducting paths of the higher vertebrate nervous system are made up of such neurons. Is it not altogether probable that the less highly specialized general visceral sensibility may be carried forward at least in part by such neuron chains? It is evident that such a pathway would not be capable of demonstration by ordinary methods of experimental degeneration. Further work is likewise needed on the details of localization of lemnisci fibers within the ventral nucleus. Moreover, there is no clear understanding of the details of thalamocortical and corticothalamic connections outside of those related to projection centers, and the thalamostriatal connections are frequently confused with thalamocortical and corticothalamic paths; these problems are all deserving of further

investigation. A study of details of the origin, course and termination of the thalamobulbar, thalamo-olivary and associated descending paths is needed for a more complete understanding of thalamic reflexes.

If the foregoing discussion has contributed to an understanding of the complexity of the diencephalon, as evidenced in phylogeny and ontogeny, and has given a greater appreciation of the problems involved, one of the purposes of this contribution will have been attained.[2]

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2. Reference has been made frequently in the text to our own observations on the avian diencephalon. This study has been completed and will appear in *J. Comp. Neurol.*, July, 1929, vol. 48, under the title "The Nuclei and Fiber Paths of the Avian Diencephalon with Consideration of Telencephalic and Certain Mesencephalic Centers and Connections."

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THE CENTRAL REPRESENTATION OF THE SYMPATHETIC SYSTEM

AS INDICATED BY CERTAIN PHYSIOLOGIC OBSERVATIONS *

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By the term sympathetic nervous system is usually meant that extensive and diffuse group of outlying neurons which are connected through white rami communicantes with the thoracic and lumbar regions of the spinal cord. Only occasionally is the expression used to include structures more central than the cell bodies of the connector or preganglionic neurons which, as Gaskell [1] and others have shown, lie in the lateral horns of the thoracic and lumbar segments of the cord. It has long been recognized that the physiologic activity of these peripheral motor neurons is entirely under the control of the central nervous system, and there is available evidence for the existence of what appear to be fairly definite central mechanisms which are concerned in the discharge of nerve impulses over preganglionic sympathetic neurons. Thus one may speak of a central representation of the sympathetic.

From the earliest times, the necessity for some connection between brain and viscera has been impressed on all who have given thought to those visceral changes which so obviously accompany strong emotional excitement. In the light of modern work, it is interesting to see how anciently and how often the opinion was expressed that the sympathetic nerves mediate the influence which the emotions exert on the viscera. Certain early writers thought of the central control of the viscera as localized in a definite part of the brain. Thomas Willis,[2] for example, placed it in the cerebellum. But there could be no real basis for any central localization of sympathetic functions until the central origins and the exact peripheral effects of the diffusely distributed sympathetic fibers were worked out. When this was finally accomplished during the second half of the last century, there soon developed a real

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1. Gaskell, W. H.: The Involuntary Nervous System, London, Longmans, Green & Company, 1920.

2. Willis, Thomas, cited by Langley, J. N.: Sketch of the Progress of Discovery in the Eighteenth Century as Regards the Autonomic System, J. Physiol. **50**:225, 1916.

knowledge of the relations which exist between the various functional groups of sympathetic fibers and the divisions of the central nervous system.

Claude Bernard was one of the most important pioneers in this aspect of the physiology of the sympathetic system. He showed that vasoconstrictor nerves are sympathetic and that through them the central nervous system exerts a constant "tonic" effect on blood vessels. He studied the ocular effects produced by section and stimulation of the cervical sympathetic. In his tendency to restrict the origin of the sympathetic to the thoracic and lumbar segments of the cord, he anticipated the classic work of Gaskell and of Langley. Bernard's contributions [3] were soon followed by German work,[4] which established as an experimental fact the ancient supposition that sympathetic nerves act on the heart. Erection of hair must have long been noticed as a symptom of emotional excitement in animals, and in 1870 Moritz Schiff [5] demonstrated the dependence of this phenomenon on the sympathetic. A few years later, Luchsinger [6] showed that the innervation of the sweat glands is sympathetic.

The fact that the sympathetic outflow from the central nervous system is confined to connector fibers which arise in the thoracic and lumbar regions of the cord was definitely established in 1886 by Gaskell.[1] As is well known, Gaskell's studies were extended by Langley,[7] who worked out the relation between white and gray rami, demonstrated the synaptic relation of preganglionic to postganglionic fibers and studied in detail the peripheral effects of sympathetic stimulation.

Of special importance to the present discussion is Langley's observation that the preganglionic fibers issuing from any one spinal nerve pass to a series of lateral ganglia, usually from six to nine in number, and never to a single segmental ganglion. This morphologic condition assures a diffuse discharge of nerve impulses over postganglionic fibers and is in marked contrast to the condition found in the parasympathetic where preganglionic fibers belonging to a definite functional group pass to ganglia situated within or close to the organ innervated, an arrangement for the discharge of impulses to single organs. When it was subsequently determined that the glandular cells of the suprarenal

3. Bernard, C.: Leçons sur la physiologie et la pathologie du système nerveux, Paris, Baillière et fils, 1863.

4. Tigerstedt, R.: Die Physiologie des Kreislaufes, Berlin, W. de Gruyter & Company, 1923.

5. Schiff, M.: Moritz Schiff's gesammelte Beiträge zur Physiologie, Lausanne, Benda, 1896.

6. Luchsinger, B.: Papers in Arch. f. d. ges. Physiol. **14**:369, 383, 1877; **22**:126, 158, 1880.

7. Langley, J. N.: The Sympathetic and Other Related Systems of Nerves, E. A. Schäfer's Text-book of Physiology, London, Pentland, **2**:616, 1900.

medulla receive a preganglionic sympathetic innervation [8] and that epinephrine on passing into the blood stream acts on any tissue in the same way as do the impulses of postganglionic sympathetic fibers,[9] it became clear that the suprarenal medulla is an integral part of the sympathetic system and that it represents another means of producing a widespread effect when the sympathetic is active. The fact that the sympathicosuprarenal system is designed to function as a whole has been pointed out by Cannon,[10] who has emphasized that the conditions under which the sympathetic tends to so act are those which demand a vigorous response to ensure the maintenance of an essential bodily state or even of life itself. Such conditions include strong emotional excitement, pain, asphyxia, exposure to cold, muscular exercise and the hypoglycemia which follows administration of insulin. The work of Cannon and his collaborators has established the emergency function of the sympathicosuprarenal system. It has received confirmation at the hands of a number of investigators working in diverse parts of the world and employing a variety of methods.[11]

Apart from its emergency function, which is characterized by a widespread discharge over all preganglionic neurons, the sympathetic carries out other duties in the animal economy. A certain fraction of the preganglionic fibers is constantly discharging, and this tonic activity is of importance in maintaining the normal level of arterial pressure, the normal heart rate, the size of the pupil, the position of the bulbus oculi, the degree of relaxation of the bronchial musculature and a few other physiologic conditions. This discharge may be broken by central inhibition or augmented by central excitation. Certain sympathetic paths such as those to the sweat glands and smooth muscle of the skin appear to be normally at rest. Apparently, certain fractions of the preganglionic outflow may discharge while others remain inactive.

From the foregoing remarks, it is apparent that the central representation of the sympathetic is of the following character: All parts of it are capable of reflex excitation and inhibition, and much of it is in constant activity; while some parts of it seem capable of acting independently of other parts, the marked tendency of the sympathetic to discharge vigorously and as a whole under conditions of stress implies the existence of some predominant central mechanism which is capable

8. Elliot, T. R.: The Innervation of the Adrenal Glands, J. Physiol. **46**:285, 1913.

9. Langley, J. N.: The Autonomic Nervous System, Part I, Cambridge, W. Heffer and Sons, 1921.

10. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton & Company, 1920.

11. Cannon, W. B.: Die Notfallsfunktionen des sympathico-adrenalen Systems, Ergebn. d. Physiol. **27**:380, 1928.

of causing a discharge of impulses over the entire series of preganglionic sympathetic neurons. With this picture in mind one may approach the actual evidence for definite central representation of the sympathetic.

BULBAR AND SPINAL SYMPATHETIC MECHANISMS

The Vasoconstrictor Mechanism.—Following Bernard's recognition of a tonic vasoconstrictor discharge from the cord, it was reported by a number of his contemporaries that section of the cord leads to a profound fall in arterial pressure. In 1870, Dittmar found that central stimulation of the sciatic induces a good reflex rise in arterial pressure after separation of the cord and medulla from the brain; he concluded that the reflex center for vasoconstriction is situated in the bulb. A relatively exact localization of the region responsible for both the tonic activity of the vasoconstrictors and their reflex discharge was accomplished by Owsjannikow [12] a year later. He used the method of successive transections of the brain stem and arrived at the conclusion that this area lies between the uppermost part of the pontile region and a point lying from 4 to 5 mm. above the calamus scriptorius. In rabbits it occupies a strip of the floor of the fourth ventricle about 4 mm. in length. In 1873, Dittmar [13] reached similar conclusions and connected the center with a group of nerve cells in the diffuse part of the superior olive. Separation of the region of Owsjannikow and Dittmar from the cord is as effective in lowering arterial pressure and pressor and depressor reflex excitability as is section of the cervical cord. Higher parts of the nervous system can and do act on the vasoconstrictor mechanism, but they are not in any sense essential for the tonic and reflex functions of that mechanism.

Following this early work done in Ludwig's laboratory at Leipzig, no further delimitation of the vasoconstrictor center was attempted until the investigations of Ranson and Billingsley,[14] who explored the floor of the fourth ventricle with a needle electrode. Application of the current at two points consistently produced marked changes in arterial pressure. One point, situated at the apex of the ala cinerea (at the lower margin of the area of Owsjannikow and Dittmar), is a pressor point; the other, a depressor point, is located in the area postrema just lateral to the obex (below the area of Owsjannikow and

12. Owsjannikow, P.: Die tonischen und reflectorischen Centren der Gefässnerven, Arb. a. d. physiol. Anstalt zu Leipzig, 1871, vol. 21.

13. Dittmar, C.: Ueber die Lage des sogenannten Gefässzentrums in der Medulla oblongata, Ber. d. Sächs. Gesellsch. d. Wiss., mat.-phys. Kl. **25**:449, 1873.

14. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions from Stimulation of the Floor of the Fourth Ventricle. Studies in Vasomotor Reflex Arcs: III, Am. J. Physiol. **41**:85 (July) 1916.

Dittmar). Sometimes a rise in pressure was obtained from the region of the facial colliculus (which corresponds to the cranial border of the area of Owsjannikow and Dittmar). It is not clear what interpretation should be attached to these observations of Ranson and Billingsley. It is possible, as the authors themselves point out, that these small areas merely represent points on the course of tracts connected with the true centers. Porter [15] has maintained that there is a vasotonic center distinct from the vasoconstrictor center, and Ranson and Billingsley made the suggestion that the region of the facial colliculus may contain such a center. It is true that in making his successive transections, Owsjannikow found that the first one which encroached on his vasomotor area caused a drop in pressure without affecting pressor or depressor reflexes. Porter's view is based on the fact that curare will increase and alcohol decrease the effects of pressor and depressor stimulation without altering the basal height of arterial pressure. As remarked by Bayliss,[16] these results do not prove the existence of separate centers, for the drugs may not act solely on the center itself. If the normal tone of the center is reflex in origin, they could affect the synapses in this or other regions in such a way that their excitability is changed for artificial, but not for natural rates of afferent impulses. If, on the other hand, the tonic activity of the center is dependent, as it may well be, on its metabolism, it is conceivable that these drugs affect the approach of sensory impulses to the center without altering the metabolism of the center itself. In regard to the existence of a separate vasodilator center, it may be said that the experiments of Ranson and Billingsley afford the only evidence which is not wholly circumstantial. In 1908, Bayliss [16] showed that the law of reciprocal innervation operates in the depressor reflex, since this involves central inhibition of the sympathetic vasoconstrictors as well as central excitation of the nonsympathetic vasodilator nerves. This suggests that the vasomotor center consists of vasoconstrictor and vasodilator elements, which may or may not be anatomically distinct. Regardless of whether there are separate vasotonic, vasoconstrictor and vasodilator centers, it is certain that a narrowly localized bulbar mechanism makes a definite connection with the sympathetic outflow to the arterioles. It is responsible for their normal tone, and its tonic activity may be increased or decreased by afferent impulses or by changes in its blood supply.

Immediately after a cervical transection of the cord, there is a great drop in arterial pressure and no vasomotor reflexes can be elicited

15. Porter, W. T.: The Vasotonic and Vasoreflex Centre, Am. J. Physiol. **36**:418 (March) 1915.

16. Bayliss, W. M.: The Vaso-Motor System, London, Longmans, Green & Company, 1923.

(spinal shock). In time, the pressure rises and, after some days, attains its normal level when large pressor responses can be obtained (recovery from spinal shock). That even the low height of pressure following cervical transection is partly due to a residuum of spinal vasotonic influence is shown by the fact that this pressure is still further lowered by splanchnic section or destruction of the cord.[4] These facts indicate that there are spinal vasoconstrictor mechanisms, subsidiary to the bulbar center, but capable, in the spinal animal at least, of independent activity. They raise the question of the contribution of the cord to the vasoconstrictor discharges of the intact animal. A definite answer to this question was given by Ranson.[17] This investigator had previously shown that in the pressor reflex as evoked from the sciatic the afferent impulses are carried along the cord in the apex of the posterior gray column. By cutting through this region on both sides at the level of the first thoracic segment, Ranson found that he was able to interrupt this afferent pathway without producing any paralysis or perceptible degree of spinal shock. If the pressor reflex were purely spinal, this lesion should not affect the reaction as evoked from the sciatic, but should abolish the reflex from the brachial. On the other hand, if the reflex were bulbar, the lesion should interrupt the spinal path connecting the sciatic afferents with the center, but leave intact the path which ascends from the afferents of the brachial plexus. Since it had been shown that a given stimulus evokes equal pressor effects from sciatic and brachial, it was possible to compare the results obtained from the two nerves. Ranson found that in each of his eight cats a good pressor reflex was obtained by faradization of the brachial nerves, but that sciatic stimulation gave no response or a slight fall of pressure in four, a slight pressor effect in three and, in one, a rise in pressure of some magnitude, but less than that obtained from brachial stimulation. These results show clearly that the normal pressor reflex arc is not complete within the cord.

The Cardio-Accelerator Mechanism.—Ever since the discovery of the cardio-accelerator nerves, it has been possible to postulate a cardio-accelerator center. On the other hand, it has not been possible to assign it any definite location. Yet the sympathetic nerves which supply the heart possess tone [18] and the capacity for reflex discharge,[19] properties which suggest a specific central representation. As a matter

17. Ranson, S. W.: New Evidence in Favor of a Chief Vaso-Constrictor Center in the Brain, Am. J. Physiol. **42**:1 (Dec.) 1916.

18. Hunt, R.: Direct and Reflex Acceleration of the Mammalian Heart with Some Observations on the Relations of the Inhibitory and Accelerator Nerves, Am. J. Physiol. **2**:395 (July) 1899.

19. Cannon, W. B., and Lewis, J. T.: The "Physiological Maximum Heart Rate" as an Artefact, Am. J. Physiol. **82**:67 (Sept.) 1927.

of fact, the medulla oblongata probably constitutes the immediate source of these discharges. Hunt [18] has reported that section of the crura cerebri does not abolish accelerator tone. While direct excitation of the floor of the fourth ventricle usually produces cardio-inhibition, this effect is replaced by acceleration after section of the vagi,[14] and the latter result is not affected by denervation of the suprarenals.[20]

Hunt [18] was the first to show the great importance of diminution of vagal tone in reflex accelerations of the heart, and both Bainbridge [21] and Brücke [22] have presented evidence that the law of reciprocal innervation holds in cardiac reflexes. These facts at once suggest that there is a single cardiac center controlling and coordinating vagal and sympathetic discharges to the heart. Furthermore, it has been suggested by Bainbridge [23] that the circulatory reflexes which occur on sensory stimulation or during muscular exercise form a group, acting as a single reflex which can be evoked by impulses from the periphery or from the cerebral cortex. At any rate, cardiac and vascular reflexes are closely interconnected; their efferent limbs are partly sympathetic, partly parasympathetic, and, if one includes the posterior root fibers concerned in vasodilatation, they are in part cerebrospinal (nonautonomic). It follows that all of the central mechanisms involved, vasoconstrictor, vasodilator, cardio-accelerator and cardio-inhibitory, are closely related physiologically, and it appears that anatomically they are connected and closely juxtaposed in the medulla oblongata.

The Reflex Mechanism for Medullisuprarenal Secretion.—Langley [7] has shown that the splanchnics receive their preganglionic fibers through white rami from the fifth thoracic to the second lumbar nerves. Consequently, the secretory fibers of the suprarenal medulla must have their cell bodies in the lateral horns of this region of the cord.

Stewart and Rogoff,[24] who have maintained that there is a constant secretion of epinephrine of unvarying amount, located the center for this activity in the upper part of the thoracic cord, but they have made the claim that neither this nor any other possible suprarenal center can be activated reflexly. They asserted that, aside from peripheral splanchnic stimulation, the only way in which they were able to bring about an increased secretion of epinephrine (as detected by their method) was

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20. Hill, L.: The Mechanism of the Circulation of the Blood, E. A. Schäfer's Text-book of Physiology, London, Pentland, **2**:1, 1900.

21. Bainbridge, F. A.: On Some Cardiac Reflexes, J. Physiol. **48**:332, 1914.

22. Brücke, E. T.: Ueber die reziproke, reflektorische Erregung der Herznerven bei Reizung des N. depressor, Ztschr. f. Biol. **67**:507, 1917.

23. Bainbridge, F. A.: The Physiology of Muscular Exercise, London, Longmans, Green & Company, 1923.

24. Stewart, G. N., and Rogoff, J. M.: The Relation of the Spinal Cord to the Spontaneous Liberation of Epinephrine from the Adrenals, J. Exper. Med. **26**:613, 1917.

by administration of strychnine or the intravenous injection of salts, agencies which cause a general excitation of the cord. Stewart [25] stated that his spontaneous constant output of epinephrine is entirely under nervous control; his quantitative estimation indicated a considerable fall in the epinephrine content of caval blood after section of the splanchnics. In short, Stewart, while affirming the tonic activity of the central mechanism connected with the secretory nerves of the suprarenal medulla, denies that this mechanism can be affected by afferent impulses. Such a center as that postulated by Stewart would indeed be unique among central nervous mechanisms. As a matter of fact, Cannon and Rapport [26] have obtained reflexly a secretion of epinephrine which they estimated to be ten times the amount which Stewart and Rogoff suppose to be the unvarying product of the glands. Furthermore, Cannon and his collaborators have repeatedly demonstrated a reflex discharge of epinephrine and, by appeal to experimental evidence, have answered the various criticisms of their method made by Stewart and Rogoff. Other investigators using various methods, including that of Stewart and Rogoff, have confirmed the observations of Cannon, while support for the contentions of Stewart and Rogoff is wholly lacking. This whole subject has recently been reviewed by Cannon.[11]

In 1912, Elliot [27] found that reflex exhaustion of the residual epinephrine of the glands was never obtained when the cord was transected above the origin of the splanchnics, but could be realized when the brain stem was divided just above the anterior corpora quadrigemina. He concluded that the reflex control of the suprarenals is associated with nervous machinery near the vasoconstrictor center. Cannon and Rapport [28] found that reflex secretion of epinephrine is not impaired by a transection of the midbrain, but is wholly abolished when the cut is just behind the inferior colliculi. This places the reflex center in the upper part of the medulla oblongata, the region containing the vasoconstrictor center. Cannon and Rapport have presented evidence that this center is subject to reflex inhibition as well

25. Stewart, G. N.: The Significance of the Suprarenal Glands in Relation to the Vital Processes, Endocrinology and Metabolism, New York, D. Appleton & Company, **2**:127, 1922.

26. Cannon, W. B., and Rapport, D.: Studies on the Conditions of Activity in Endocrine Glands: VI. Further Observations on the Denervated Heart in Relation to Adrenal Secretion, Am. J. Physiol. **58**:308 (Dec.) 1921.

27. Elliot, T. R.: The Control of the Suprarenal Glands by the Splanchnic Nerves, J. Physiol. **44**:374, 1912.

28. Cannon, W. B., and Rapport, D.: Studies on the Conditions of Activity in Endocrine Glands: VII. The Reflex Center for Adrenal Secretion and Its Response to Excitatory and Inhibitory Influences, Am. J. Physiol. **58**:338 (Dec.) 1921.

as to reflex excitation, and that a balanced effect may be produced by simultaneous elicitation of these opposed reflexes. One is reminded of similar phenomena which Bayliss obtained in his study of depressor and pressor reflexes and, taken together, the results of these two lines of work afford additional evidence of the inseparability of sympathetic and suprarenal mechanisms. Contributory evidence for a bulbar control of medullisuprarenal secretion was given by Carrasco-Formiguera,[29] who reported that sugar puncture will cause a liberation of epinephrine into the blood.

Bulbar Control of Carbohydrate Mobilization.—Although Claude Bernard's classic experiments on sugar puncture gave proof of the possibility of a nervous control of carbohydrate mobilization mediated by the sympathetic (splanchnics), neither they nor similar experiments performed by later workers have resulted in the localization of a definite bulbar sugar center. The area from which the effect can be produced is large, and a similar temporary hyperglycemia can be evoked by injury of many parts of the brain. Another method of approach to this problem would be to investigate the possibility of inducing reflex rises in blood sugar with various parts of the central nervous system excluded, but this has not been undertaken in any systematic way, and until further data are available, it is impossible to make a definite assertion that the bulbar region contains the reflex center. At present it can only be said that since the floor of the fourth ventricle contains a central mechanism for the tonic and reflex excitation of many processes controlled by sympathetic nerves, it is likely that there is a bulbar mechanism for the carbohydrate mobilization which can be induced by splanchnic discharge. The probability of this is strengthened by the fact that sugar puncture leads to a discharge of epinephrine which, as many have shown, acts on the liver to produce hyperglycemia. Griffith's analysis [30] of the factors which produce reflex hyperglycemia has shown that secretion of epinephrine plays a rôle at least equal in importance to that of the direct nervous discharge to the liver.

Other Bulbar and Spinal Sympathetic Mechanisms.—There are certain processes under sympathetic control which have not yet been shown to possess any localized bulbospinal representation. These are secretion of sweat, erection of hair, inhibition of gastro-intestinal motility, pupillodilatation and a few other effects.

Sympathetic pupillodilatation, however, has received some attention in this connection. In 1851, Budge and Waller [3] were led to believe

29. Carrasco-Formiguera, R.: The Production of Adrenal Discharge by Piqûre, Am. J. Physiol. **61**:254 (July) 1922.

30. Griffith, F. R.: Reflex Hyperglycemia: A Study of the Carbohydrate Mobilization Effected by Afferent Crural, Sciatic and Vagus Stimulation, Am. J. Physiol. **66**:618 (Nov.) 1923.

that the pupillodilator fibers of the cervical sympathetic arise from the last two cervical and first two thoracic nerves. Budge described the corresponding segments of the cord as a "centrum cilio-spinale" and found that after separation of this part of the cord from the rest of the central nervous system stimulation of any of its posterior roots would cause widening of the pupils. The result was probably due to spread of stimulating current to the anterior roots. In the long controversy which followed Budge's work, the bulk of evidence was against the existence of such a center. Anderson [31] obtained a slow dilatation reflexly from the isolated cord, but Karplus and Kreidl [32] could not get this effect after cooling the upper part of the cervical cord. The latter investigators admit that ocular reflexes which are dependent on the cervical sympathetic may be mediated through the bulb, but they regard the hypothalamus as the normal reflex center for such changes.[33]

A number of workers have shown that the isolated spinal cord is capable of discharging sympathetic impulses to the sweat glands. Luchsinger,[6] who was one of the first to show that the sudorific nerves have a sympathetic origin, demonstrated this fact, and more recently Riddoch [34] has found that in men suffering complete transection of the cord the slightest and most diverse stimuli will induce profuse sweating from the regions of the skin innervated by the isolated part of the cord. This hyperhidrosis constitutes a part of the mass-reflex characteristic of these cases. Yet neither the results of the earlier investigator nor those of Riddoch actually prove that the spinal cord is more than a conductor of sweat impulses in the normal intact animal. In regard to the behavior of the isolated cord in man, the mass-reflex is simply an indication that in the absence of the higher control spinal reflexes suffer the loss of their local signature. The physiologic state of such a cord is far removed from the normal.

The literature yields no good evidence of a bulbar sweat center, but higher control of this function is certain, and that phase of the subject will be considered presently.

THE HIGHER CONTROL OF THE SYMPATHETIC SYSTEM

From what has been said in the preceding section, it is apparent that bulbospinal mechanisms suffice for many tonic and reflex activities of the sympathetic. But it is possible that higher parts of the central

31. Anderson, H. K.: Reflex Pupil-Dilatation by Way of the Cervical Sympathetic, J. Physiol. **30**:15, 1904.

32. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: III Mitteilung. Sympathicusleitung im Gehirn und Halsmark, Arch. f. d. ges. Physiol. **143**:109, 1911.

33. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: IV Mitteilung. Arch. f. d. ges. Physiol. **171**:192, 1918.

34. Riddoch, in Head, H.: Studies in Neurology, London, H. Froude, 1920.

nervous system may subserve similar functions, and it is a fact that the lower mechanisms are influenced from above. It is therefore necessary to devote some attention to the nature of the higher control.

The Relation of the Cerebral Cortex to the Sympathetic.—As already stated, the sympathetic has long been regarded as the connecting link by which the cerebral activities underlying emotional excitement act on the viscera. In general, it has been assumed that these activities occur at the highest level in the brain, namely, the cerebral cortex.

Shortly after the discovery of cortical excitability in 1870, physiologic literature became replete with reports of the localization in the cortex of almost every bodily function. Among the effects obtained during that orgy of cortical stimulation were ones which one recognizes as being under sympathetic control. Good accounts of this work are given by Schäfer [35] and by Ferrier.[36] A study of the original reports has convinced me that many of the effects which were produced are to be accounted for on the basis of spread of strong stimulating currents to subcortical regions or to production of cortical epilepsy in which a widespread and unphysiologic discharge occurs. The effects were rarely associated with stimulation of a single cortical area. Furthermore, in many instances the animals were only curarized, and in the absence of a true anesthetic, there was ample opportunity for them to give reflex visceral responses to the slightest dural or other purely sensory stimulation. When weaker current strengths were used with light anesthesia, a rise in arterial pressure was a common mode of response, and in such cases it may be that the foregoing criticisms do not hold. But it is significant that such results were obtained most commonly from the motor cortex, and they may be classed with those involuntary changes which accompany the performance of voluntary movements and which Bainbridge [23] has suggested result from an "irradiation" of pyramidal (voluntary) impulses on bulbar centers. Widening of the pupils by cervical sympathetic discharge was one of the visceral changes most frequently reported by the early explorers of the cortex, but more recently Parsons [37] has found that, in the absence of the epileptic condition, it is obtained only from those cortical areas which are concerned in eye movements. On the whole, it seems fair to apply to the earlier observations a criticism made by Ferrier that "they are merely complications and not the results of localized cortical stimulation."

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35. Schäfer, E. A.: The Cerebral Cortex, Text-book of Physiology, London, Pentland, **2**:697, 1900.

36. Ferrier, D.: The Functions of the Brain, London, Smith, Elder and Company, 1886.

37. Parsons, J. H.: On Dilatation of the Pupil from Stimulation of the Cortex Cerebri, J. Physiol. **26**:366, 1901.

The method of cortical stimulation has most certainly failed to demonstrate a definite sympathetic representation in the cortex cerebri.

Many who have sought evidence for a cortical control of the sympathetic have felt that the pronounced activity of that system during emotional excitement is to be explained on the basis of a cortical discharge. But it has been pointed out elsewhere [38] that while it is reasonable to suppose that the neural processes underlying emotional consciousness are indeed cortical, it does not follow that the bodily changes which make up emotional behavior are due to a nervous discharge of cortical origin. The behavior attending the major emotions, fear and rage, is primitive, energetically purposive and common to the various members of the mammalian class. Its occurrence is dependent on the native inheritance of the animal and illustrates the fact that for the physiologist an emotion is a typical reaction pattern. The behavior of an enraged cat is no more complex and no more the result of experience than are its postural and righting reflexes which have been so well described and analyzed by the late Professor Magnus of Utrecht. These considerations suggest that the reaction is dependent on the older divisions of the central nervous system. There is much experimental evidence to show that this is actually the case.

When a dog or cat is deprived of its cerebral hemispheres, the capacity for the exhibition of emotional behavior is by no means abolished. After complete removal or disconnection of all parts of the cerebral cortex and with injury to the corpora striata and the dorsal part of the thalamus, Goltz [39] kept his dog alive over eighteen months. The general behavior of the animal has been described frequently and is well known. Its emotional activity was confined to a reaction, capable of regular elicitation, which closely resembled the picture of rage seen in a normal dog. The same was true of the similar dog described by Rothmann.[40] Dusser de Barenne [41] has prepared and studied in the chronic condition two hemisphereless cats which showed marked emotional responses to various disturbances, innocuous as well as mildly harmful to them; merely lifting the animals caused energetic movements of defense and those reactions so characteristic of the angry cat—

38. Bard, Philip: A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490 (April) 1928.

39. Goltz, F.: Der Hund ohne Grosshirn, Arch. f. d. ges. Physiol. **51**:570, 1892.

40. Rothmann, H.: Zusammenfassender Bericht über den Rothmannschen grosshirnlosen Hund nach klinischer und anatomischer Untersuchungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:247, 1923.

41. Dusser de Barenne, J. G.: Récherches expérimentales sur les fonctions du système nerveux central, faites en particulier sur deux chats dont le neopallium a été enlevé, Arch. néerl. de Physiol. **4**:31, 1920.

spitting, growling and erection of hair. The trivial and often irrelevant nature of the conditions which would evoke the rage-reaction in these four animals is noteworthy. It was induced in Goltz' dog by pinching the skin or by taking it from its cage, a procedure which invariably caused a violent protest in spite of the fact that it was the usual signal for feeding and would have been agreeable to a normal dog. Snarling and growling were obtained in Rothmann's dog by gentle scratching of the back, and the presence of a fly on the creature's nose sent it into a fit of fury. It is disappointing that in the observations on the emotional behavior of these animals only one sympathetic symptom is mentioned, namely, the erection of hair in the case of the cats. Other superficial signs of sympathetic discharge were undoubtedly present, but were evidently overlooked. A year and a half ago, through the kindness of Dr. Stanley Cobb, I was afforded the opportunity of observing the behavior of a chronic decorticate cat (neopallium removed) which closely resembled one of Dusser de Barenne's animals. Certain aspects of the behavior of this animal have been reported by Schaltenbrand and Cobb.[42] It exhibited well marked signs of anger when disturbed. Pinching its tail lightly caused not only hissing with lowering of the head and arching of the back, but also erection of the hair of the back and tail, distinct retraction of the nictitating membranes, pupillodilatation and separation of the lids (exophthalmos), all signs of sympathetic discharge.

The observations on chronically decorticate animals suggested to Cannon and Britton[43] the possibility of using an acute decorticate preparation for the study of the emotional activation of the sympathetic. They found that after disconnection of the cortex from the brain stem, in cats, there appears on removal of the anesthetic " a group of remarkable activities such as are usually associated with emotional excitement—a sort of sham rage." A prominent feature of this quasi-emotional state consists of signs of widespread sympathetic activity; it is attended by erection of hair, profuse sweating from the toe-pads, high arterial pressure and discharge of epinephrine from the adrenal medulla. Bulatao and Cannon[44] described the hyperglycemia associated with the activity and showed that medullisuprarenal secretion plays a major rôle in its production. Experiments which are being carried

42. Schaltenbrand, G., and Cobb, S.: Demonstration of Decorticated Cats, Arch. Neurol. & Psychiat. **17**:407 (March) 1927.

43. Cannon, W. B., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XV. Pseudaffective Medulliadrenal Secretion, Am. J. Physiol. **72**:283 (April) 1925.

44. Bulatao, E., and Cannon, W. B.: Studies on the Conditions of Activity in Endocrine Glands: XVI. The Rôle of the Adrenal Medulla in Pseudaffective Hyperglycemia, Am. J. Physiol. **72**:295 (April) 1925.

out at present by me indicate that the high heart rates of this sham rage are attained by a direct sympathetic discharge to the heart, reinforced and supplemented by medullisuprarenal secretion.

The observations on decorticate animals are consistent in showing that removal of the hemispheres renders an animal unusually disposed to exhibit a behavior which is primitively emotional and comparable to that which enables the normal animal to meet the critical situations of life. They give strong support to the view that the nervous mechanisms for the *expression* of rage are subcortical. They indicate that the part played by the cortex in the production of the bodily changes which accompany strong emotion is one which may actually involve a decrease rather than an increase in the influence exerted by the cortex on subcortical mechanisms. The excessiveness and the easy elicitation of the rage-reaction of decorticate animals gives it the appearance of a release phenomenon, and it is perhaps best explained on the basis of the view first advanced by Hughlings Jackson and more recently elaborated by Head [45] to the effect that the cortex normally holds in check those activities of the lower and more archaic centers which would seriously interfere with its more discriminative reactions. The expression of emotional excitement is just this sort of activity, and in the case of chronically decorticate animals release from cortical control would seem to the chief factor in producing the tendency to react excessively; there the chronicity of the behavior precludes its being the product of any sort of "irritation."

The Diencephalic Representation of the Sympathetic.—Some idea of the subcortical level responsible for the emotional activity of the decorticate animal can be gained from experiments in which cerebral ablation has not been followed by such behavior. While it is true that pseudaffective reflexes are shown by the decerebrate animal (midbrain transected) in both the acute and the chronic condition, it is important to distinguish them from the activities which constitute the sham rage of the decorticate preparation. In the former, as exemplified by the experiments of Bazett and Penfield,[46] the activity consists of isolated items of behavior and is typically brought forth by a stimulus ordinarily associated with some habitual mode of response. In the investigation of Woodworth and Sherrington,[47] these reflexes were evoked by strong stimulation of afferent fibers and were described as having a certain "width of coordination," but "they never amount to an effective action

45. Head, H.: Release of Function in the Nervous System, Proc. Roy. Soc., Ser. B, **92**:184, 1921.

46. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as well as the Acute Condition, Brain **45**:185, 1922.

47. Woodworth, R. S., and Sherrington, C. S.: A Pseudaffective Reflex and Its Spinal Path, J. Physiol. **31**:234, 1904.

of attack or escape." On the other hand, the sham rage of the decorticate animal in the chronic as well as the acute condition is elicited by trifling disturbances of any kind, is astonishingly intense and possesses a width and energy of expression that makes it unmistakably the counterpart of intense fury in the normal animal. The central region which is responsible for this more general, more energetic and more easily produced affective behavior must lie below the cortex and above the lower half of the mesencephalon.

With these points in mind, I [38] undertook an investigation directed toward the delimitation of the part of the brain stem responsible for the sham rage of the decorticate cat. It was felt that not only would this elucidate the neural basis for this emotion but also might advance knowledge of the central representation of the sympathetic. The fact that it is in rage that the sympathetic especially exhibits its tendency to discharge vigorously and as a whole made it appear that the region sought represents a predominant central coordinating mechanism for the sympathetic system, a center which when active causes a discharge over the entire series of sympathetic preganglionic neurons. In a series of forty-six successful acute experiments, it was found that the sham rage occurs regularly after ablation of the hemispheres, corpora striata and the cranial half of the diencephalon. But it invariably failed to develop when the brain stem was transected at the caudal extremity of the diencephalon or through the cranial portion of the mesencephalon. The typical activity developed after removal of the dorsal and cranial parts of the diencephalon. As a result of this investigation it becomes possible to state that the discharge of nervous impulses which evokes the extraordinary motor activity of the decorticate preparation is conditioned by central mechanisms which lie within an area comprising the caudal half of the hypothalamus and the most ventral and most caudal fractions of the corresponding segment of the thalamus.

The motor activities of the sham rage are both somatic and visceral. Struggling, snarling, clawing and lashing of the tail are combined with erection of the hair, dilatation of the pupils, retraction of the nictitating membranes, exophthalmos, profuse sweating and enormous increments in arterial pressure and heart rate. The last mentioned group of activities are due to a widespread discharge of sympathetic impulses and they are apparently occasioned by the activation of the same central mechanism which is responsible for the concomitant activity in skeletal muscle. These two aspects of the total activity are not separable and together form an integrated reaction. This fact, however, in no way curtails the force of the argument that these experiments demonstrate the existence of a diencephalic representation of the sympathetic.

The evidence for a diencephalic representation of the sympathetic obtained from this study of the decorticate rage is in accord with earlier physiologic work. In 1900, Karplus and Kreidl [48] first found that in cats electrical stimulation of an hypothalamic point, lateral to the infundibulum, will produce maximum dilatation of the pupils, separation of the lids and retraction of the nictitating membranes. They showed [49] that these ocular effects are mediated by the cervical sympathetic, that they are due to stimulation of a true hypothalamic center and that no other parts of the diencephalon except the hypothalamus yield them. They mentioned that the stimulation caused sweating from all four feet and, in subsequent papers,[50] reported rises in arterial pressure. Houssay and Molinelli [51] have presented evidence that medullisuprarenal secretion may be provided by hypothalmic stimulation.

Certain facts relating to the regulation of body temperature support the view that there is a diencephalic control of the sympathetic system. On the other hand, it is established [52] that the integrity of a region of the brain stem lying above the middle of the mesencephalon and below the corpora striata is essential for the maintenance of a constant body temperature, and there is strong if not conclusive evidence that the heat-regulating center is in the hypothalamus.[53]. On the other hand, it is well known that erection of hair, ruffling of feathers, constriction of peripheral vessels, mobilization of sugar and increased medullisuprarenal secretion [54] occur when the homoiothermic animal is exposed

48. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I Mitteilung. Zwischenhirnbasis und Halssympathicus, Arch. f. d. ges. Physiol. **129**:138, 1909.

49. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: II Mitteilung. Ein Sympathicus-Zentrum im Zwischenhirn, Arch. f. d. ges. Physiol. **135**:401, 1910.

50 Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: VII Mitteilung. Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und innerer Sekretion, Arch. f. d. ges. Physiol. **215**:667, 1927.

51. Houssay, B. A., and Molinelli, E. A.: Centre adrénalino-sécréteur hypothalamique, Compt. rend. Soc. de biol. **93**:1454, 1925.

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to a low environmental temperature. It is reasonable to suppose that this activation of the sympathetic has its immediate source in the diencephalon, for this part of the brain appears to contain the neural mechanism essential for temperature control.

It is significant that exposure to cold and strong emotional excitement call forth similar bodily changes. Restlessness, trembling, shivering, and especially those visceral activities which denote a widespread sympathetic discharge are common to both conditions. Under both conditions these reactions represent an effort on the part of the animal to cope with a critical situation and they afford excellent examples of the emergency function of the sympathetic. It now appears that in both instances they are dependent on activity in the diencephalon. This suggests that the diencephalic representation of the sympathetic constitutes that dominant central mechanism the existence of which is so plainly implied by the tendency of the sympathetic to discharge vigorously and as a unit under conditions of stress.

The following sketch of the central representation of the sympathetic is suggested by the physiologic evidence at hand. The preganglionic neurons which have their origins in the lateral horns of the thoracic and lumbar segments of the cord are normally under the control of supraspinal influences. This control may be exerted continually and so lead to a steady discharge of impulses to postganglionic neurons or it may become evident only when the controlling mechanism is set into action by circulatory, metabolic, reflex or other influences. The tonic discharge is subject to both central excitation and central inhibition. Functionally similar groups of preganglionic fibers are normally under the control of their respective bulbar centers which suffice for the tonic and reflex sympathetic discharges. Higher levels are not essential for their activity, but are capable of influencing them. Superimposed on these bulbospinal mechanisms is a dominant mechanism located at the base of the diencephalon and capable of causing a simultaneous discharge over the entire series of preganglionic neurons. This diencephalic mechanism is activated at times of stress, in emergencies, and is responsible for the widespread discharge which then occurs. The various activities of the sympathetic nervous system appear to have a neural basis of this sort. The picture is hazy, and it will require the combined efforts of physiologist and morphologist to clear it.

TONUS IN SKELETAL MUSCLE IN RELATION TO SYMPATHETIC INNERVATION*

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A number of facts have led physiologists to look on tonus in skeletal muscle as a function wholly distinct from other types of contraction. Many believe that it calls into play a different mechanism from that which produces the simple twitch evoked by artificial stimulation.

Decerebrate rigidity, a state in which the extensor muscles of the limbs remain for a long time in sustained contraction with extraordinary freedom from fatigue, has been taken as the most perfect example of tonus, and has for several reasons been held to exemplify those properties wherein tonus differs from ordinary contraction. In the first place the economy of metabolism and the lack of fatigue and of heat production are so marked, as compared with contraction of the same strength artificially induced, as to suggest the employment of a different mechanism. In the second place, the property of plasticity, as noted by Sherrington, whereby a decerebrate limb retains approximately the posture imposed on it by passive flexion or extension, the extensor muscles maintaining nearly the same tension at various degrees of contraction, suggests a property like that of the so-called "catch muscle" in the adductor mechanism of bivalve molluscs. This "catch muscle," which is distinct from the muscle causing motion, has the power to maintain a given degree of adduction against great tension for long periods of time without appreciable fatigue. Dynamically it resembles a vise in that it resists great force, but does no work. The superficial resemblance between the plasticity of the decerebrate limb and that of the molluscan adductor has led some physiologists to suppose that the tonus of the decerebrate limb possesses a property of plasticity which is a distinct function from contractility. Furthermore, the failure to detect action currents in some types of sustained contraction of skeletal muscle has led many to the view that the tonic type of contraction is one which does not involve the electric response characteristic of artificial tetanus and voluntary contraction.

The work of Boeke (1911, 1919) and those who have followed him apparently established the innervation of certain skeletal muscle fibers

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by sympathetic nerve fibers. Although the extensive review of Hines brings out the confusing and often contradictory character of the testimony, her summary of the literature, as well as Cobb's (1925) and Fulton's (chapter 16), supports the view that in some skeletal muscles there are striated fibers so innervated. On the other hand, Hinsey was led by a critical survey of previous work and a careful anatomic investigation to doubt the existence of sympathetic innervation in any mammalian skeletal muscle fibers.

The finding of sympathetic nerve endings in skeletal muscles naturally led to a search for their function, and in conjunction with the baffling nature of tonus and the apparent need of a special mechanism for its maintenance, predisposed many physiologists to the theory of a tonic function in these nerves. De Boer reported a loss of "tonus" on cutting the sympathetic nerves, and took this observation as a clue to their function. However, the observation by both Cobb (1918) and Dusser de Barenne (1916) that decerebrate rigidity persists after cutting the sympathetic nerves to the limb involved, showed that this type of tonus, at least, does not depend on sympathetic fibers. Indeed the lack of any constant difference between the muscles of the two sides when the sympathetic nerves were cut on one side only, either in the decerebrate or intact animal, in Cobb's experiments, and his failure to evoke contraction on stimulation of the sympathetic trunks, rendered it doubtful if tonic activity of any sort is mediated by these nerves.

Langelaan advanced a theory that there are two distinct components of tonus in skeletal muscle, "contractile tonus" and "plastic tonus." Hunter and Royle assumed that Langelaan's theory was well founded and that this distinction was valid. They further assumed that both types of tonus were present in decerebrate rigidity. On this assumption, they undertook to determine whether plastic tonus depended on the sympathetic nerve fibers. A few of Hunter's experiments on birds and goats appeared to show an impairment of the so-called plastic element in tonus on cutting the sympathetic nerves, without impairment of the so-called contractile element. The experiments on goats were too few to warrant final conclusions on a problem in which so many possible sources of error and confusion are present. The experiments on birds, together with confirmatory experiments by Kuntz and Kerper (1926), strongly suggest some such division of function between cerebrospinal and sympathetic nerves as Hunter inferred. Coombs and Tulgan have also reported experiments tending to confirm those of Hunter and Royle by showing diminution of tonus in animals on interruption of sympathetic innervation. Kuré reported observations on the diaphragm, which seem to support this theory; but they do not appear to be very clearcut and should be confirmed before the conclusion is finally accepted. Hines pointed out logical fallacies in Hunter's interpretation of his experi-

ments. Moreover, even if his conclusion were established for birds, it would not be safe to assume that the neuromuscular organization in this respect is the same in birds and in mammals. The attempt to relegate plastic and contractile functions respectively to red and white or fine and coarse muscle fibers has been shown by Cobb (1925), Fulton and Hines to lead only to confusion. Anatomically, it is established that red fibers, as well as white, receive somatic innervation. Physiologically, it was shown by Hay that red fibers do not act like the "catch" mechanism, but contract like the white fibers, only more slowly. This forces the advocates of dual functions to place the contractile and plastic functions in the same fiber.

Royle, assuming that his own and Hunter's experiments proved that the plastic element of tonus is mediated by the sympathetic nerves, undertook to introduce the operation of ramisection in human surgery, with the idea that, by removing the plastic element in tonus, relief of the condition of spastic paralysis would be effected. He claimed to have produced marked and lasting relief by this operation and his claim is reinforced by those of Stewart and Kuntz.

Ranson (1926), also assuming the validity of Langelaan's theory of separate plastic and contractile functions, experimented with the application of nicotine and chloral hydrate to the spinal ganglia in decerebrate animals. Finding that both these drugs caused a decrease in decerebrate rigidity before they blocked conduction in the dorsal roots and thereby abolished rigidity altogether, and failing to find any considerable loss of tonus on sympathectomy, he concluded that the plastic element in tonus was mediated by synapses in the spinal ganglia from which the tonic impulses passed antidromically to the muscle, and that only the plastic tonus was abolished by the initial stages of the action of the drugs, while contractile tonus, being mediated by motor nerves, was abolished only when conduction in the dorsal roots ceased altogether. Thus, though he accepts the idea of dual function, he differs from Hunter as to the anatomic structure whereby the plastic function is mediated.

In the theories quoted it is not made clear whether contractile tonus is supposed to be a wholly distinct function from ordinary contraction. If so, the theories would assign to muscle three distinct functions: phasic contraction, contractile tonus and plastic tonus. I shall consider the question as to whether there is any sound reason for the assumption of dual or triple function in muscle.

It should be noted that Langelaan's theory of distinct plastic and contractile elements in tonus is a speculation based in part on misunderstanding of the work of previous observers. His representation of Lucas's observations is misleading in two respects. He cited Lucas as having found three different kinds of contractile substance in skeletal muscle, whereas Lucas (1907) clearly stated that he found three excita-

ble substances, one of which he identified as the nerve fibers within the body of the muscle—obviously not to be classed as a contractile substance. The contraction of the muscle was the same in Lucas's experiment, no matter what excitable substance was acted on by the stimulus. Elsewhere the stepwise increase in the muscle twitch with gradually increasing stimuli, from which Lucas (1909) deduced the all-or-none law of muscular contraction, was redrawn by Langelaan as a smooth curve to fit an irrelevant mathematical formula. By such methods, he laid the foundation for his theory.

His principal direct evidence for the assumption of dual function in muscle is a record in which a reflex contraction showed a much more gradual onset than did a twitch evoked by a single stimulus applied to the motor nerve. All the work of Sherrington (frequently misquoted in support of dual function) points to the view that all reflex contractions, whether of abrupt or gradual onset, or sustained as in tonus, are built up of individual responses of the same fundamental character as that appearing in the twitch. The recent work of Liddell and Sherrington and of Fulton and Liddell furnishes strong evidence that decerebrate rigidity consists essentially of a sustained stretch reflex, the adequate stimulus to the intramuscular receptors being tension, and involves no other type of muscular response than that which appears in the simple twitch. Fulton (p. 385) contended that "all forms of contractile tension, whether static or phasic, are due to all-or-none contractions of individual muscle units under the integrative control of the somatic nervous system." It should be noted that Sherrington never maintained that plasticity was a separate function from contractility in tonus. He merely called attention to the superficial similarity between the plastic decerebrate limb and the adductor apparatus of the mollusc, in the ability of the muscle in each case to maintain a given degree of shortening irrespective of the amount of tension. He also furnished evidence tending to show that this behavior was due to proprioceptive reflexes; i.e., reflexes initiated by afferent impulses arising within the muscle involved (also Fulton, chapter 17).

Ranson's experiments, taken to support the theory of distinct contractile and plastic elements in tonus, are also capable of at least two other interpretations which involve nothing more than the single and clearly demonstrable function of contraction in skeletal muscle. Fulton (p. 405) suggested that the initial effect of nicotine, when applied to the spinal ganglia, might be the stimulation of afferent fibers which would partially inhibit decerebrate rigidity. Such an effect might be mistaken for the abolition of the alleged plastic element in tonus. Another interpretation of Ranson's observations is based on the probability that afferent impulses follow each other at such high frequency that each occurs in the relative refractory phase following its predecessor

and therefore is subnormal (Lucas, Forbes and Olmsted). Under these conditions the partial narcotization of that portion of the afferent root comprising the spinal ganglion would suffice to block those afferent impulses arising in the intramuscular receptors which reflexly cause decerebrate tonus, before it sufficed to block the full-sized afferent impulses set up by artificial stimulation of the nerve. Thus, while reflexes could still be artificially induced, there would be a partial loss of tonus. At all events, Ranson gives no proof of a qualitative change in tonus; the observed difference may have been entirely quantitative. One may conclude that the theory of contractile and plastic tonus as two distinct functions in muscle is absolutely without foundation.

Gessler and Hansen reported that the performance of definite work by human subjects in the long-lasting, so-called psychic, non-fatiguable postures, is accompanied by the same expenditure of energy in the state of complete hypnosis as it is in the normal waking state. This postural phenomenon had been taken by some as an example of tonus, distinct from contraction, but the authors concluded that the consumption of energy is evidence in favor of the tetanic character of this form of contraction, and does not support the conception of a special tonus function in cross-striped muscle similar to that found in certain postural muscles of invertebrates.

Some physiologists, struck by the apparent contrast between tonus and contractions causing motion, have given great vogue to the theory that tonus is unattended by action currents, thereby sharply differentiating it from those ordinary contractions evoked by artificial stimuli. Recently, the work of a number of investigators, including Dusser de Barenne (1911), Buytendyk and others (Forbes and Cattell), has proved that decerebrate rigidity does not depend solely on an action-currentless type of contraction. The clasp reflex of the male frog was at one time taken to be an example of action-currentless contraction, but Wachholder and Lullies have shown that with sufficiently careful experimentation it is possible to detect action currents in this contraction as well as in other forms of sustained contraction of central origin. The apparent absence of action currents was largely due to the quiescence of the muscle, an illusion of strong tonus being created by the ready response of the muscle to stretch. When this stretch reflex was induced, action currents appeared (Adrian, 1925).

Liljestrand and Magnus induced a sustained contraction by injection of tetanus toxin, and in this condition found an apparently complete absence of action currents. Ranson (1928) made similar observations and emphasized the absence of action currents in the contractions so produced. He found that if the motor nerve was cut before the contraction developed, it did not develop at all, but if severed after the development of the tetanus contraction, the muscle did not relax. The

latter stage is a contracture clearly not maintained by nerve impulses. Both Ranson and Fulton (p. 414) infer a direct action of the toxin on the muscle. But Ranson's experiments seem to show that since this contracture does not develop unless it is initiated by nerve impulses, the local effect of the toxin must be, at most, a minor factor. The most probable inference is that the contraction, induced at first by nerve impulses, develops through fatigue a state of contracture. It is a familiar classroom experiment to stimulate a muscle to the point of extreme fatigue, and to observe in this condition the enormous slowing of relaxation. This effect is associated with the acidity caused by activity. It is conceivable that tetanus toxin acts on the neuromuscular junctions in such a way as to abolish their normal propensity for developing fatigue earlier than the muscle, and thereby protecting it from overstimulation. The prolonged contraction evoked by the persistent discharge of nerve impulses from the center would then produce a degree of acidity which would prolong the relaxation time almost indefinitely, and a contracted state without further functional response would be the result.

Pereira attempted to show that the "postcontraction" in man spontaneously following the cessation of a prolonged, voluntary, isometric contraction (Salmon, Kohnstamm) was a case of action-currentless contraction, but repetition of his experiments with proper controls (Forbes, Baird and Hopkins) resulted in refutation of nearly every conclusion that he drew, and clearly established the fact that postcontraction was exactly like voluntary contraction as regards the action currents which accompany it.

Thus, with the exception of the pathologic contracture induced by toxins, all forms of sustained contraction in skeletal muscle which have yet been carefully scrutinized are characterized by electric responses (Adrian, 1925). These action currents mark the functional response evoked by artificial stimulation, whether applied directly to muscle or to the motor nerve. They are characteristic of ordinary reflex and voluntary contraction. In so far as decerebrate rigidity manifests action currents resembling those of ordinary contraction, it appears to involve the same contractile mechanism.

There are certain fundamental theoretical difficulties in the way of accepting either the concept of dual function of plasticity and contractility in skeletal muscle fibers or the conception of the action-currentless type of tonic contraction. When a nerve or muscle fiber is stimulated, a functional response in the form of a propagated disturbance is set up and sweeps over the fiber from the point of stimulation. The exact nature of the disturbance is unknown, but this much is certain, that the energy of propagation comes from the tissue, not from the stimulus; that the available energy is momentarily depleted by the

transmission of the disturbance, leaving the tissue refractory to further stimulation until recovery has occurred, and that therefore the response obeys the all-or-none law (Adrian, 1914; Kato; Davis, Forbes, Brunswick and Hopkins). Dynamically, the functional response is unlike a sound wave or other form of vibratory energy in an inert conductor, but resembles rather the burning of a fuse or train of gunpowder. In spite of the many differences between nerve fibers and muscle fibers, these fundamental principles apply alike to both. The activity of a tissue which responds in this way cannot be subject to qualitative variation due to any difference in the type of stimulation any more than the burning of a fuse can be modified by a change in the flame which first ignites it. Any change in the nature of the response must depend on a change in the state of the tissue, such as would be induced by fatigue or an alteration of the physicochemical environment of the fiber. Dual function would demand the presence in the fiber of two distinct, excitable structures. Such an arrangement has been suggested in the theory of contractility of sarcoplasm as an independent mechanism distinct from the fibrils. As Cobb has shown (1925, p. 528), there is no physiologic evidence of sarcoplasmic contraction; the theory is a purely speculative hypothesis. There is, then, no clear evidence, either anatomic or physiologic, that there is more than one type of functional response of which muscle is capable. Abundant evidence reveals the essential identity in the nature of responses evoked artificially and by natural means. For instance, the action currents in a motor nerve or muscle appear to have the same character and time relations, whether set up by direct stimulation of the motor nerve or by reflex excitation (Forbes and Gregg); the afferent impulses of muscle sense are characterized by action currents indistinguishable from those set up by direct stimulation of the nerve trunk (Forbes, Campbell and Williams; Adrian, 1926; Adrian and Zotterman). All these facts point strongly to the view that the functional response of a nerve or muscle fiber is always the same in kind, and that the differences between tonic activity and transient contraction lie in the sequence and distribution of individual responses among the numerous fibers which make up the nerve or muscle in question.

Pollock has recently argued in favor of a plastic mechanism in skeletal muscle, distinct from the contractions and relaxations demonstrably correlated with motor nerve impulses. He and Davis have reported experiments on decerebrate animals in which, when a muscle was passively stretched and a tonic labyrinthine reflex produced, the muscle shortened with decrement of pull; "but if coincident with production of the tonic labyrinthine reflex at the height stretch the muscle was further stretched no shortening occurred and the muscle remained 'pulled out'." (Pollock, p. 222.) The opinion is expressed that this

was not due to inhibition, and a change in the physical property of muscle is inferred, due to some unknown mechanism quite apart from the presence or absence of motor nerve impulses. The muscle is said to undergo an alteration which is likened to a change from rubber to gum.

The nature of this observation suggests that it may have been an instance of the "lengthening reaction" previously described by Sherrington (1909) and shown by him and by Fulton (p. 431) to be a phenomenon of reflex inhibition, and like all other established phenomena of decerebrate rigidity, dependent on the number and distribution of motor nerve impulses and the resulting contractile responses. On the other hand, Pollock and Davis stated that the tracings from their muscle were similar after the posterior roots had been cut. Whatever lengthening was obtained thereafter was obviously not due to reflex inhibition. The question arises whether their observation could not be interpreted in terms of the viscous-elastic properties of muscle described by Gasser and Hill, without the assumption of any new function distinct from its ordinary contractile response.

Thus far I have considered the experiments supporting the views of Hunter and Royle and the theoretical reasons for doubting them. These theoretical objections are reinforced by the following experimental evidence. Kanavel, Pollock and Davis removed the abdominal sympathetic chain on one side in cats, and at various intervals thereafter decerebrated them by the anemia method. No difference, quantitative or qualitative, was found between the limbs on the operated and unoperated sides. They also interrupted the sympathetic innervation of spastic limbs in human subjects without apparent results. Meek and Crawford performed unilateral sympathectomy in a series of dogs and found no demonstrable effects on tonus. Coman, experimenting on both dogs and cats, used three methods of attack. His results are summarized as follows:

1. Stimulation of the sympathetic innervation to the foreleg failed to cause any tonic reaction.

2. Complete deprivation of sympathetic innervation to the foreleg failed to influence the normal development of tone either before or after decerebration.

3. Complete deprivation of somatic motor innervation to the foreleg was followed by complete abolition of tone in that leg both before and after decerebration.

A series of experiments was undertaken by Cannon, O'Connor, Hopkins and Miller and myself, with the hope that by use of quantitative methods of experimentation we might detect small changes in tonus, if any existed. Hunter and Royle emphasized the need of a lapse of time—several days or even weeks—after interrupting the sympathetic innervation before the full effect of the operation developed.

As was pointed out by Cobb (1925), Meek and Crawford and Adrian (1926), this fact in itself would suffice to rule out the immediate effect of sympathetic nerve impulses as the direct cause of tonus or of any component of tonus. Any such delayed effect would lead to the view that its cause must be in some secondary effect such as circulatory changes in the muscle. In order to bring out such an effect if it existed, the animals in our series were decerebrated at various intervals after sympathectomy, up to eighty days. In eleven of these the fore limb on one side was deprived of its sympathetic innervation by removal of the stellate ganglion; in the other six, the abdominal sympathetic chain of one side was removed. In three of the animals we performed decerebration first, and then, after observation whether or not decerebrate rigidity was symmetrical on the two sides, performed sympathectomy and observed the immediate effect of it, if any. In all the rest of the series, sympathectomy was performed first aseptically, and after a period of from three to eighty days the animal was decerebrated, and rigidity on the two sides quantitatively studied by means of spring balances to measure the tension of muscle, and protractors to measure the angles of the elbow or ankle joints.

These experiments showed, in the first place, that if precautions are taken to avoid confusion due to the influence of asymmetrical posture (shown by Magnus and de Kleijn to modify decerebrate rigidity), tonus will usually be approximately symmetrical on the two sides in a decerebrate animal, prior to sympathectomy, and a fairly satisfactory basis can thus be found for testing the effect of operation. Uncontrolled changes in decerebrate rigidity, however, occur occasionally and render the basis of comparison unreliable. A large number of consistent results would be needed to warrant conclusions.

As to the effect of sympathectomy, the results of these experiments were by no means uniform. Comparison of the operated limb with its mate usually showed almost perfect symmetry, that is, no appreciable difference. Sometimes there was a little less rigidity on the operated side, sometimes a little more. Averaging the measurements of the entire series showed slightly less rigidity on the operated side, but this difference was small compared with the individual fluctuations in both directions making up the average. Typical curves of tonus from these experiments are shown in figures 1 and 2. Figure 3 shows an animal in which the sympathectomized limb, instead of being less rigid, consistently showed more rigidity than its mate. The conclusion from these experiments was that, if there was any loss of tonus in consequence of the operation, it was insignificant. We found it extraordinarily easy to produce an illusion of decreased tonus by manipulating the limb on which we concentrated our attention, more than its mate. This effect is presumably due to the operation of the "lengthening reac-

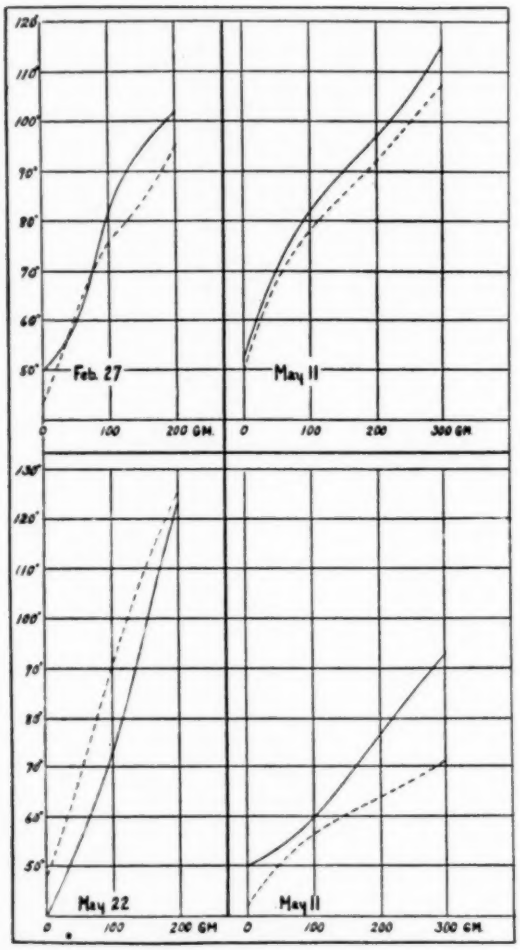

Fig. 1.—Curves correlating elbow flexion with the flexing force applied in the stellate experiments. The abscissae represent tension applied to the wrist perpendicular to the ulna; the ordinates, degrees of flexion; the solid line, the operated limb; the broken line, the control. In the section dated February 27, three days after operation, the measurements were made one hour after decerebration; on May 11, seventy-six days after operation, the upper curves were obtained twenty minutes and the lower curves three hours after decerebration; on May 22, seventy-four days after operation, the measurements were made one and one-half hours after decerebration.

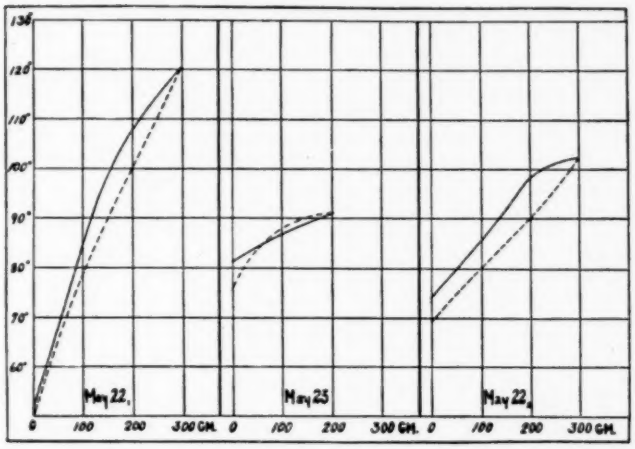

Fig. 2.—Curves correlating ankle flexion with the flexing force applied in the abdominal sympathetic experiments. The abscissae represent tension applied to the foot perpendicular to the metatarsal bones; the ordinates, degrees of flexion; the solid line, the operated limb; the broken line, the control. In the section dated May $22_{,1}$ four days after operation, the measurements were made forty minutes after decerebration; on May $22_{,2}$ seventy-three days after operation, fifty minutes after decerebration, and on May 23, sixty-eight days after operation, one hour after decerebration.

Fig. 3.—Appearance two hours after decerebration, six days after the operation on the left stellate. Persistent maintenance of greater rigidity in operated limb was noted.

tion" (Sherrington, 1909). Certainly, decerebrate rigidity persisted at least approximately undiminished after sympathectomy, and continued to manifest its plastic features.

Ranson and Hinsey, in a series of decerebrate cats, previously sympathectomized, also found no constant difference between operated and normal limbs.

Since these results were published, Mortensen, Friedbacher and Quade have reported a series of careful experiments on goats. This is especially interesting, since Hunter's experiments were also performed on goats, and the contention was made that these animals are better adapted to bringing out the effects of sympathectomy than the more usual laboratory animals. Mortensen, Friedbacher and Quade found that the changes in limb tonus due to neck posture, reported by Magnus and de Kleijn, were very marked in the goat and a slight asymmetry of position, therefore, confused the result. After making careful allowance for this factor, they found in their series no constant or significant difference in tonus between the unoperated and operated sides. Even before the researches of Coman, Forbes, Cannon, O'Connor, Hopkins and Miller, Ranson and Hinsey, and Mortensen, Friedbacher and Quade had been published, Adrian (1926), in the course of what is perhaps the clearest and most logical discussion of this subject, said, "On the experimental side then, the balance of published evidence seems overwhelmingly against the view that the sympathetic sends out impulses which have a *direct* controlling effect on posture, the length or the plastic tone of the limb muscles, an effect comparable to that of the cerebro-spinal impulses." With the addition of these four researches, the preponderance of negative evidence has become even greater than it was when Adrian discussed the problem.

As to the surgical operation of ramisection, several surgeons have been convinced of its efficacy in properly selected cases of spastic paralysis. On the other hand, Crothers (1925), who made a careful study of a number of patients operated on by Royle, was convinced that the beneficial results were either nonexistent or else dependent entirely on extraneous factors, such as reeducation, good nursing and after-care. Stewart reported favorable results of the operation in a number of cases. His patients undoubtedly showed improvement, but it is perhaps significant that one unsuccessful case in table 3 is explained with the footnote, "has not come for reeducation." If successful results depend on reeducation, and in the absence of this are not secured, one wonders if the operation in itself accomplished anything unless perhaps through the psychologic effect of making the patient feel that something important had been done. That such a heroic form of mental suggestion might well be eliminated, especially if sufficient care and skill be devoted to the reeducation, is strongly suggested by the conviction

expressed by one physician of extensive experience on seeing motion pictures of a patient before and after the operation of ramisection, that he could frequently duplicate the result by medical procedures alone.

The researches of Orbeli and Nakanischi may perhaps open a way to reconcile the apparently conflicting testimony of various observers in this field (Martin). Orbeli reported that stimulation of the sympathetic nerves simultaneously with stimulation of the somatic nerves adds nothing to contraction until fatigue appears. With the onset of fatigue, sympathetic stimulation increases the contraction evoked by somatic stimulation. The sympathetic effect shows a much longer latency than muscular contraction evoked by stimulation of the motor nerve, a latency which approximates that of the action of the sympathetic nerves on the heart.

Nakanischi, working on frogs, found that stimulation of the sympathetic nerves alone caused no contraction of the skeletal muscle, but when stimulation of the sympathetic was added to maximal stimulation of the somatic nerve the resulting contraction was augmented. The effect was the same whether the augmenting stimulus was applied to the sympathetic nerve before it joined the somatic nerve or whether the stimulus was applied to the combined nerve distal to the point of junction. Stimulation of the somatic nerve, alternately proximal and distal to the point where the sympathetic nerve joins it, produced identical contractions until the strength of stimulus was increased to a certain value, taken to be the threshold of the sympathetic fibers. Increasing the strength of stimulus beyond this value caused augmentation of contraction when the stimulus was distal to the point of junction, whereas no change was found when the stimulus was proximal to this point. The author does not appear to have completely excluded the possibility that the augmentation was due to somatic fibers damaged at a point distal to the distal electrodes, so remote from the proximal electrodes that no strength of stimulus applied there was able to excite them, and stimuli at the distal electrodes could only do so when strong enough to cause a considerable current spread along the nerve. On the other hand, the close similarity of the responses obtained by stimulation distal to the point of junction and by simultaneous stimulation of the separate somatic and sympathetic nerves renders this interpretation improbable and strongly supports Nakanischi's contention that the sympathetic fibers exert an augmenting effect on contraction already established by somatic fibers.

These observations suggest that the nerve impulses reaching the muscles by the sympathetic fibers act on them in a different manner from the ordinary somatic motor nerve impulses. Apparently they do not stimulate the muscle; that is, they do not cause contraction. Yet it is conceivable that at the sympathetic nerve endings a chemical effect

of some sort is produced which alters the state of the muscle and, in some way yet to be explained, counteracts the tendency to fatigue, and possibly under other conditions, may augment contraction evoked through the somatic nerves. Recent observations by Campos, Cannon, Lundin and Walker have shown that epinephrine, whose action in general simulates the effect of sympathetic nerve impulses, although ineffective when given before exercise, can prolong to a remarkable degree the capacity of exhausted animals to continue at work.

Chemical responses to stimulation are well known to occur in many different types of cell, as for example, all the gland cells and many of the less differentiated cells involved in repair processes following injury. The migration of phagocytic cells to the site of an inert foreign body can hardly be explained without the assumption that mechanical contact of the foreign body with the adjacent cells stimulates them to produce some substance which attracts the phagocytes by chemotropism (Forbes, 1910). There are also the striking experiments of Loewi (1921) on humoral transmission of vagus action. These important results have apparently been confirmed by Brinkman, Kahn and de Oliviera Frias. In general, they show that fluid, perfused through a heart being subjected to vagus inhibition, acquires the property of conferring an inhibitory effect on another heart through which it is subsequently perfused. Loewi (1926) has gone so far as to draw inferences as to the chemical nature of the vagal substance produced in this way. If these effects are definitely established they serve as another striking instance of chemical effects resulting from stimulation of the autonomic nerve. More than this, they furnish an instance of a chemical effect occurring in a muscle tissue specialized primarily for contractile response. There still remains a doubt, however, as to the interpretation of Loewi's experiments. The observations of Asher and Scheinfinkel suggest that the result may be due not to a direct effect of the vagus nerve impulses, but to physicochemical changes in the fluid surrounding the muscle fibers caused by a decrease in their contractile activity.[1]

It should be noted that Wastl was unable to confirm Orbeli's observation. Fulton (p. 411) suggested a possible explanation for her negative results and was inclined to favor the view that Orbeli's conclusions are valid. On the other hand, Porter (1926), finding that epinephrine does not augment tonic contraction in the decerebrate cat, and arguing from the fact that the effect of sympathetic excitation is

1. Recent observations by Hinsey and Gasser (Am. J. Physiol. **87**:368, 1928), dealing with a slow contraction, apparently without action currents, in a degenerated nerve-muscle preparation, evoked either by stimulation of undegenerated afferent fibers in the nerve trunk or by chemical means, are suggestive in connection with the type of function which Orbeli's and Loewi's results indicate. Their bearing on normal muscle is difficult to interpret.

elsewhere simulated by epinephrine, concluded that sympathetic nerve impulses have no effect on tonus. In view of such doubts, it is perhaps premature to accept Orbeli's conclusions as established without confirmation by further experiments.

If such an effect as Orbeli described is indeed a reality, it is conceivable that its loss may explain the observations of Hunter, Royle, Kuntz and Kerper, and others who have found changes in tonus following sympathectomy. Impairment of the ability to resist fatigue would tend to diminish the amount of tonic contraction, especially under conditions in which fatigue is likely to develop. It may be that the positive observations have been made under conditions which caused more fatigue than existed in the negative observations. On the other hand, Campos, Cannon, Lundin and Walker found no increased susceptibility to fatigue in running dogs whose hind limbs were deprived of their sympathetic innervation. Uncertainty as to the conditions favoring fatigue, complexity of the circulatory changes resulting from sympathectomy, and possibly other obscure phenomena are factors that tend to confuse this problem and render it difficult to determine why some experiments are positive and some negative.

One of the most baffling features of tonus has been the great economy of energy. In decerebrate rigidity, tension is maintained for a long time without visible fatigue, and with little metabolism or heat production, as compared with tetanic contraction induced either by voluntary effort or artificial stimulation. This economy has been a major consideration in predisposing physiologists to consider tonus something distinct from other types of sustained contraction. In an earlier communication (Forbes, 1922), it was suggested that this economy might be effected if different groups of fibers took up the load in rotation, each group of fibers possibly being relieved by synaptic fatigue in the reflex arc before the fibers themselves became fatigued, and the next group in turn being called into activity through the proprioceptive mechanism of the stretch reflex. Adrian and Bronk have just reported some new observations on tonus which give fresh insight into the mechanism involved. Their new technic has enabled them to observe directly the rhythm of discharge of impulses in a single motor nerve fiber. Applying this to the limb reflexes, they have found that a vigorous contraction, in the case of the crossed extension reflex, is mediated by a series of about eighty impulses per second. In the tonic reflexes, on the other hand, the individual fiber conducts between five and ten impulses a second. Some recent isometric observations, made by Dr. H. Davis in the Harvard laboratory (unpublished), show that a mammalian skeletal muscle, when fatigued, maintains tension more economically if stimulated at a frequency of twenty-five per second than at fifty per second.

In the muscle taken as a whole, it is clear from electromyographic studies (Buytendyk, Forbes and Cattell) that the individual fiber groups are responding quite out of phase with each other; that is, there is no visible synchronism of response at any such slow frequency as five or ten a second. It is conceivable that the economy may be aided by this asynchronism of individual responses in adjacent fibers. If one applies five maximal stimuli per second to the motor nerve, the muscle soon fatigues. But in this case it contracts as a whole and has time to relax and lengthen after each response; at the next response it must shorten again and do physical work. If, after the contractile effort of each individual fiber, it is prevented from lengthening by friction with an adjacent fiber already in a contracted state, the contraction will be practically isometric, and the wasteful lengthening will be eliminated. The slow relaxation of the red fibers, as compared with the white, increasing the overlapping in time of contractile tension of adjacent fibers, would serve the purpose of economy.

One may conclude from this survey of the evidence that in skeletal muscle, instead of three functions, ordinary contraction, contractile tonus and plastic tonus, there is one function—contraction—built of all-or-none releases of contractile energy, but so arranged in time and space by the various reflex influences which play on the motor centers as to appear sometimes phasic, sometimes tonic and sometimes plastic.

SUMMARY

1. The evidence from a great variety of research leads to the conclusion that in skeletal muscle there is only one type of contraction, and that the apparent difference between tonus and other forms of contraction is superficial and not fundamental; also that tonus depends for its sustained character and economy of energy on the sequence of individual responses and their distribution among the numerous fiber groups which constitute the entire muscle.

2. There is no foundation for the view that the sympathetic nervous system controls a plastic element in tonus functionally distinct from so-called contractile tonus. All contraction, tonic or phasic, disappears when the somatic motor nerves are cut. Sympathetic nerve fibers, when stimulated, do not cause contraction; their severance does not lead to disappearance of tonus. A great deal of research has been made to test the alleged tonus-maintaining function of the sympathetic nerves. The great majority of the studies made apparently have shown complete absence of any such effect, and some of them have revealed sources of error which may well explain the few positive results that have been reported.

3. It is doubtful whether sympathetic innervation has any appreciable effect on tonus. If it has, the effect must be due either to cir-

culatory changes or to some obscure physicochemical effect of excitation through this channel, analogous perhaps to secretion. There is some evidence that such an effect exists, not causing contraction, but tending to allay fatigue and facilitate the continuance of contraction evoked through the somatic motor nerves. Although the evidence in favor of such an effect is strongly suggestive, there are still doubts as to its interpretation, and it is probably premature to accept the effect as definitely established.

4. The surgical operation of ramisection for the relief of spastic paralysis rests on a wholly inadequate physiologic basis, a basis built of speculation and misinterpretation of experimental evidence. Reeducation has been regarded as an important sequel to this operation. In view of the physiologic evidence, it is perhaps reasonable to conclude that reeducation is the only therapeutic agent that has any real effect in these cases.

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THE PARASYMPATHETIC CONTROL OF MUSCLE TONUS *

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Orthodox physiology does not satisfactorily account for normal muscle tonus nor for the various types of hypertonus and contracture. The inadequacy of the explanations of these phenomena, which can be deduced from the conception of a single motor innervation and the all-or-none law, has led to the formulation of theories of dual innervation and a special holding mechanism. The theory which has attracted most attention is that skeletal muscle receives a tonic innervation from the sympathetic nervous system. But, fairly recently, another theory was formulated by Frank,[1] namely, that tonic impulses are conveyed to the muscles antidromically over parasympathetic fibers in the dorsal roots. At the time this ingenious idea was conceived it had much in its favor. The pseudomotor phenomenon, a slow tonic contraction produced by stimulation of the dorsal roots after degeneration of the ventral root fibers, is closely allied to antidromic vasodilation and to the contracture produced by acetylcholine, which is a powerful parasympathetic stimulant. Furthermore, it is generally believed that section of the dorsal roots not only abolishes normal muscle tonus but prevents the development of rigidity after decerebration and after the injection of tetanus toxin. When my attention was directed to the idea some five years ago, it seemed to me to offer a solution to the tonus problem. Since that time, my associates and I have been engaged in putting the hypothesis to the test in a variety of experiments. Although we have accumulated considerable data bearing on the problem, we have found no convincing evidence in favor of Frank's hypothesis.

PSEUDOMOTOR PHENOMENA

Under certain conditions, muscles can be made to undergo a slow tonic contraction by the stimulation of what are apparently sensory fibers. Examples are the Vulpian-Heidenhain contraction of the tongue, and the pseudomotor phenomenon in the muscles of the limbs. In 1863,

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1. Frank, E.: Berl. klin. Wchnschr. **57**:725, 1920; Arch. f. exper. Path. u. Pharmakol. **90**:149, 1921.

Vulpian and Philippeaux [2] showed that after section and degeneration of the hypoglossal nerve the tongue could be made to contract by stimulation of the lingual nerve. This was due to stimulation of the chorda tympani fibers; stimulation of the lingual above its junction with the chorda was without effect. Heidenhain [3] confirmed these observations and showed that the reaction reached its height about one week after section of the hypoglossal nerve and remained at its maximum until the end of the third week, when it began to decrease. The contraction caused the tongue to deviate toward the side of stimulation. The threshold was high, and only stimuli much stronger than those necessary to activate a motor nerve like the hypoglossal were effective. The contraction differed from that produced in the normal tongue by the stimulation of the hypoglossal nerve in that the latent time was much greater and the response was slow and sustained. Single induction shocks were without effect, or produced only a slight localized fibrillary twitching. Rapidly repeated strong induction shocks were required.

In 1894, Sherrington [4] obtained a similar response in the muscles of the limbs by stimulating their sensory fibers several weeks after they had been deprived of their motor innervation. He cut the motor and sensory roots of the sixth and seventh lumbar and the first and second sacral nerves proximal to the spinal ganglia; forty-two days later, he stimulated the peroneal nerve with strong induction shocks. There occurred a slow dorsal flexion of the ankle and extension of the toes. The contraction was slow to develop and persisted for several seconds after cessation of the stimulus. Since the response did not occur if the roots had been cut on the distal instead of the proximal side of the spinal ganglia, he concluded that the fibers concerned had their cells of origin in the spinal ganglia. The possibility that the contraction was due to the escape of electrical current along the nerve to the muscle was ruled out by the fact that the contraction occurred when the electrodes were located at a point on the nerve 20 cm. from the muscle.

These pseudomotor phenomena are not caused by the stimulation of sympathetic fibers contained in the nerves. Van Rijnberk [5] found that after degenerative section of the hypoglossal nerve stimulation of the cervical sympathetic trunk produced no effect on the tongue. This independence of sympathetic fibers also holds for the pseudomotor phenomenon in the muscles of the limbs. Van Rijnberk found that after section of the spinal nerve roots stimulation of the abdominal sympathetic caused no response in the muscle.

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2. Vulpian and Philippeaux: Compt. rend. Acad. d. sc. **56**:1009, 1863.
3. Heidenhain, R.: Arch. f. Physiol., Suppl., 1883, p. 133.
4. Sherrington, C. S.: J. Physiol. **17**:211, 1894-1895.
5. Van Rijnberk, G.: Arch. néerl. de physiol. **1**:257 and 726, 1917.

Which Fibers Must Be Cut in Order to Prepare the Muscle for Pseudomotor Reactions?—It is clear from van Rijnberk's work that sympathetic fibers are not concerned in any way. In all the earlier work on the pseudomotor reaction in the muscles of the limbs the motor and sensory roots were both cut proximal to the spinal ganglia. Van Rijnberk thought that if the motor roots alone were cut the reaction could not be obtained. This was interpreted as evidence that fibers, capable of inhibiting the response, leave the spinal cord over the dorsal roots and must be cut and degenerated before the reaction can be obtained. Hinsey and Gasser,[6] however, have been able to obtain the pseudomotor phenomenon in the cat's leg after section of the motor roots alone. This eliminates the necessity for postulating the existence of these inhibitory fibers in the dorsal roots. It would therefore appear that degeneration of the motor fibers is in itself sufficient to sensitize the muscles.

What Are the Fibers, Stimulation of Which Causes the Pseudomotor Phenomenon?—The chorda tympani is such a mixture that an answer to this question could scarcely be obtained by studying the Vulpian-Heidenhain phenomenon. In the case of the muscles of the limbs the problem is approaching solution. The degenerated motor fibers necessary for sensitization rule out the ventral root. Van Rijnberk has eliminated the sympathetic fibers. There remain only fibers of dorsal root origin, and Sherrington has shown that the fibers which are responsible for the phenomenon have their cells of origin in the spinal ganglia. In the dorsal roots are found myelinated fibers of all sizes and many that are unmyelinated. Sherrington thought that the large myelinated fibers going to the muscle spindles might be responsible and that the responses were due to the contraction of the intrafusal muscle fibers. But it does not seem probable that the few intrafusal fibers, widely separated as they are through the belly of the muscle, could produce the tensions up to 1 Kg. which Hinsey and Gasser obtained from the cat's gastrocnemius. Furthermore, the proprioceptive fibers are all large or medium sized fibers, and there is good reason to believe that the fibers which cause the contraction are small.

Hinsey and Gasser[6] called attention to the fact that the high threshold of stimulation of the fibers responsible for the pseudomotor phenomenon is convincing evidence that these fibers are small. They have investigated this question with the aid of the cathode ray oscillograph. With this delicate instrument they were able to show that rapidly repeated stimuli of a strength sufficient to activate all of the large and medium sized fibers, as evidenced by the record of their action

6. Hinsey, J. C., and Gasser, H. S.: Am. J. Physiol. **87**:368, 1928.

potentials given by the oscillograph, did not cause the contraction. Only when the strength of the induction shocks was raised sufficiently high to bring the small fibers into action did the contraction occur. The effective stimuli were of about the same strength as those required to produce vasodilation, and they [7] were definitely able to show that these are very small fibers.

It is known that the dorsal roots contain many small myelinated and unmyelinated fibers (Ranson [8]), but Hinsey [9] was unable to trace any of these to endings in the muscle fibers. They could be traced along the blood vessels and occasionally were seen in the intramuscular connective tissue close to muscle fibers. If it is true that they do not end on muscle fibers, then the contraction produced by their stimulation must be, as Heidenhain [3] suggested, pseudomotor.

Relation of the Pseudomotor Phenomenon to Vasodilation.—It has been suggested that the response might be due to vasodilation, since the nerves which produce the pseudomotor reaction also cause vasodilation, and since both these responses have a high threshold of stimulation and a long latency. But Heidenhain demonstrated that the movement was not due to engorgement of dilated vessels with blood because the movement occurred in an excised tongue. There is, however, a close association between the pseudomotor phenomenon and vasodilation. Acetylcholine and nicotine (injected intra-arterially) are both powerful vasodilators (Ranson and Wightman [10]), and they both cause a contracture of denervated muscle similar to the pseudomotor reaction. But there are some vasodilator drugs, like histamine [11], which do not cause shortening of denervated muscle. This close relation between vasodilation and the pseudomotor phenomenon raises the question: In what way could vasodilator fibers on the vessels bring about the contraction? It is improbable that the muscle fibers are stimulated by the action potentials of the sensory nerve fibers in their neighborhood, as suggested by Langworthy,[12] because, if this was the case, one would expect to obtain the response from the large sensory fibers which have much greater action potentials than the small fibers; it is known that these large fibers are not effective. Hinsey and Gasser [6] suggested another possible explanation. "If the vasodilation itself

7. Hinsey, J. C., and Gasser, H. S.: The Nerve Fibers Involved in Posterior Root Vasodilatation, to be published.

8. Ranson, S. W.: J. Comp. Neurol. **22**:159, 1912.

9. Hinsey, J. C.: J. Comp. Neurol. **44**:87, 1927.

10. Ranson, S. W., and Wightman, W. D.: Am. J. Physiol. **62**:414, 1922.

11. Gasser, H. S., and Dale, H. H.: J. Pharm. & Exper. Therap. **28**:287, 1926; ibid. **29**:53, 1926.

12. Langworthy, O. R.: Bull. Johns Hopkins Hosp. **35**:239, 1924; J. Comp. Neurol. **86**:273, 1924.

should take place according to Loewi's [13] humoral transmission theory, it is conceivable that the intermediate substance might also be pharmacodynamically active on skeletal muscle sensitized by denervation, although not so on a normal muscle."

In favor of this humoral transmission theory is the fact that the action current in the pseudomotor phenomenon is wave free. In a nerve-muscle tetanus, a record of the action currents shows waves corresponding in period to the stimuli. Schäffer and Licht [14] found that the pseudomotor phenomenon and acetylcholine contracture in the tongue are both accompanied by the same electrical change, namely, a large monophasic variation as recorded by the string galvanometer. The record of the pseudomotor phenomenon was as free from waves as the drug contracture. Hinsey and Gasser [6] examined the pseudomotor phenomenon in the muscles of the limb with the cathode ray oscillograph and showed that during contracture no waves of potential appeared corresponding to the stimuli.

This smooth waveless action current is additional evidence against the idea that the pseudomotor phenomenon is brought about by the direct stimulation of muscle by nerve fibers. If the contraction was brought about by accessory endings of the dorsal root fibers on muscle fibers or by the escape of the action potentials of sensory fibers, the action current should show waves corresponding in phase to the stimuli applied to the nerve; however, if the action is an indirect one, the absense of these waves could be understood.

Relation of the Pseudomotor Phenomena to the Drug Contractures.—When isolated frog muscle is immersed in a solution containing a small amount of nicotine a tonic shortening is induced. Langley [15] has shown that the nicotine acts just as well after section of the nerve. Hence it acts beyond the nerve ending in what he called the neural region of the muscle, the receptive substance of Langley. Acetylcholine acts in a similar way. Riesser and Neuschlosz [16] stated that the prolonged shortening of the frog's gastrocnemius caused by both of these drugs is due to a stimulation of Langley's receptive substance and is prevented by curare, atropine and procaine hydrochloride. Furthermore, when injected into the blood stream nicotine and acetylcholine cause a slow and rather prolonged shortening of denervated mammalian muscle. Since acetylcholine is a powerful parasympathetic stimulant, Frank,

13. Loewi, O.: Pflüger's Arch. f. d. ges. Physiol. **189**:239, 1921.

14. Schäffer, H., and Licht, H.: Arch. f. exper. Path. u. Pharmakol. **115**: 180, 1926.

15. Langley, J. N.: J. Physiol. **48**:73, 1914.

16. Riesser, O., and Neuschlosz, S. M.: Arch. f. exper. Path. u. Pharmakol. **92**:254, 1922.

Nothmann and Hirsch-Kauffmann [17] have considered its action as evidence of the existence of a special parasympathetic innervation. Gasser and Dale [11], however, found that the facts when considered critically do not support such a conclusion.

I have already called attention to the fact that the action current of the pseudomotor phenomenon, like that of the acetylcholine contracture, is wave-free. Another point of similarity between acetylcholine contracture and the pseudomotor phenomenon is that both are inhibited by epinephrine (Hinsey and Gasser [6]). Acetylcholine, being a parasympathetic stimulant, and epinephrine, which inhibits both, being a sympathetic stimulant, one could argue that both were parasympathetic phenomena. Frank, Nothmann and Hirsch-Kauffmann [17] found that acetylcholine contracture was antagonized by large doses of scopolamine (up to 15 mg.). Hinsey [18] was able to inject 7 mg. of scopolamine hydrobromide without causing any considerable decrease in the response to acetylcholine and without any effect on the pseudomotor phenomenon. This dose is far in excess of that required to block any known parasympathetic responses. This large dose of scopolamine was injected intra-arterially in such a manner that it was all carried with the blood stream into the one leg the reactions of which were to be tested. Hinsey also found that 2 mg. of atropine was ineffective in blocking the pseudomotor phenomenon.

Gasser and Dale [11] pointed out that acetylcholine, in addition to its power to reproduce parasympathetic effects in involuntary muscle, has the ability to imitate the action of nicotine on ganglion cells, and presented reasons for believing that the contracture which it produces on denervated muscle is due to its nicotine-like action, rather than to its efficacy as a parasympathetic stimulant.

The Effect of Parasympathetic Drugs on Muscle Tonus.—In this connection it should not be overlooked that both atropine and scopolamine tend to decrease the hypertonus in paralysis agitans and in the postencephalitic parkinsonian syndrome. According to Marinesco and Nicolesco [19], the rigid muscles become softer, the cogwheel phenomenon diminishes, passive movements become easier and the tendon reflexes become more lively. This has been interpreted by Kuré and Shinosaki [20] as due to the paralyzing action of these drugs on hypothetic parasym-

17. Frank, E.; Nothmann, M., and Hirsch-Kauffmann, H.: Berl. klin. Wchnschr. **1**:1820, 1922; Pflüger's Arch. f. d. ges. Physiol. **197**:270, 1923; ibid. **198**:391, 1923.

18. Hinsey, J. C., and McNattin, R. F.: Anat. Rec. **42**:50, 1929.

19. Marinesco, G., and Nicolesco, M.: Rev. neurol. **1**:207, 1927.

20. Kuré, K., and Shinosaki, T.: Ztschr. f. d. ges. exper. Med. **44**:791, 1924-1925.

pathetic fibers ending in skeletal muscle. Schäffer [21] has shown that Tiegel's contracture is exaggerated by parasympathetic stimulants (physostigmine and pilocarpine) and inhibited by atropine and epinephrine. No satisfactory explanation has yet been given of the effect which these drugs appear to have on these states of abnormally increased tonus.

Huggett and Mellanby [22] injected 2 mg. of atropine intravenously without affecting muscle tonus either in the intact anesthetized cat or in the decerebrate preparation. A similar absence of effect was observed after the intravenous injection of pilocarpine. It will be seen that the pharmacologic evidence of the existence of parasympathetic tonus fibers supplying skeletal muscle is far from convincing. The well established facts are not easily harmonized with one another. One can say only that at present no satisfactory explanation can be given of the action which various parasympathetic stimulant and depressant drugs have on skeletal muscle.

THE RÔLE OF THE DORSAL ROOTS IN MUSCLE TONUS

Recently, Frank [1] formulated the theory that tonic impulses are conveyed to the muscles antidromically over parasympathetic fibers in the dorsal root. This theory received considerable attention because it has been believed since the time of Brondgeest [23] that section of the dorsal roots causes a loss of tonus in the muscles supplied by the divided roots. The conception of tonus as a proprioceptive reflex has been extensively elaborated by Sherrington [24] and his associates. Most of the observations reported by these workers, however, could as easily be explained on Frank's hypothesis as by the proprioceptive reflex theory.

The most direct approach to this problem is to cut the dorsal roots and note the effect on tonus. If either Frank's hypothesis or the proprioceptive reflex theory is correct, one would expect marked and persistent atonia to result from such an operation, and it is generally believed that such is the result. That this belief is to a certain extent erroneous has been shown by a study which I [25] made recently of the rôle of the dorsal roots in muscle tonus. The literature was there reviewed in some detail. Here it need only be said that Trendelen-

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21. Schäffer, H.: Pflüger's Arch. f. d. ges. Physiol. **185**:42, 1920.

22. Huggett, A. St. G., and Mellanby, J.: J. Physiol., 1925, vol. 60; Proc. Physiol. Soc.

23. Brondgeest, P. J.: Arch. f. Anat. u. Physiol. 1860, p. 703.

24. Sherrington, C. S.: Quart. J. Exper. Physiol. **2**:109, 1909; Brain **38**:191, 1915.

25. Ranson, S. W.: The Rôle of Dorsal Roots in Muscle Tone, Arch. Neurol. & Psychiat. **19**:201 (Feb.) 1928.

burg [26] cut the dorsal roots supplying the wings in pigeons without altering the tonus of the musculature of the wing. Bickel,[27] Mott and Sherrington [28] and Kopczýnski [29] seem to have obtained hypertonia and contracture in the deafferented limbs of some of their animals. Liljestrand and Magnus [30] found that during the first few days after section of the dorsal roots of one brachial plexus, the triceps was entirely flaccid but retained the capacity for active movement. After about one week, the muscle again acquired tonus, and this increased with time. Foerster [31] advocated cutting the dorsal roots as a cure for spastic paralysis, but the operation has not been very successful (Steinke [32]).

Hypertonia After Section of the Dorsal Root.—In my experiments [25] on cats, when one hind leg had been completely deafferented by section of the dorsal roots close to the spinal cord, that leg became atonic for only about twenty-four hours. Subsequently, an overaction of the extensor muscles nearly always developed and usually also an increased resistance to passive flexion. After from two to four weeks these evidences of hypertonia largely disappeared. During the period of hypertonia the deafferented leg was adducted and extended, and was quite useless. Later, when the cat was again able to walk, it had difficulty in flexing this leg, which tended to be dragged with the dorsal side of the foot down. This inability to use the limb gave the appearance of a paresis. Contracture, a permanent shortening of the extensor muscles which persists after section of the motor nerves or even after the death of the animal, not infrequently developed in muscles deafferented by section of the dorsal roots proximal to the spinal ganglia. For some reason not easily understood, removal of the spinal ganglia delayed or prevented the development of the hypertonia and contracture in the deafferented muscles.

Decerebrate Rigidity.—This is a condition of heightened tonus in the antigravity muscles, especially in the extensor muscles of the limbs, caused by transection of the mesencephalon. To the extent that this heightened tonus is maintained by impulses traveling out over the dorsal roots, it should be decreased or abolished by section of the dorsal roots. I [25] found, in agreement with Sherrington, that section of the

26. Trendelenburg, W.: Arch. f. Physiol., 1906, p. 1.

27. Bickel, A.: Pflüger's Arch. f. d. ges. Physiol. **67**:299, 1897.

28. Mott, F. W., and Sherrington, C. S.: Proc. Roy. Soc. **57**:481, 1895.

29. Kopczýnski, S.: Polnisch. Arch. f. biol. u. med. Wissenschr., Lemberg **3**: 99, 1907.

30. Liljestrand, G., and Magnus, R.: Pflüger's Arch. f. d. ges. Physiol. **176**: 168, 1919.

31. Foerster, O.: Deutsche Ztschr. f. Nervenh. **58**:151, 1918.

32. Steinke, C. R.: Surg. Gynec. Obst. **27**:55, 1918.

dorsal roots in a decerebrate cat caused the immediate disappearance of the rigidity. However, this must be attributed, at least in part, to shock. If, after section of the dorsal roots, an animal was allowed to recover for several weeks before decerebration, decerebrate rigidity was slow to develop. But after the lapse of time varying from thirty minutes to several hours, a tremulous oscillating type of rigidity developed. This is contrary to the observations of Sherrington,[24] but in agreement with those of Liljestrand and Magnus.[30] The last mentioned authors found that a certain amount of rigidity developed in deafferented muscles after decerebration. Pollock,[33] in experiments conducted in collaboration with Davis, also obtained decerebrate rigidity in deafferented muscles.

The Crossed Extensor Reflex.—Another phenomenon, which offers an opportunity to test the significance which the dorsal roots, and any parasympathetic fibers that they may contain, have for tonus, is the crossed extensor reflex. The response has been studied chiefly in decerebrate and spinal preparations. Normal waking cats do not show this reflex. Even in waking cats, however, I [25] have found the reflex well developed in deafferented limbs. Pinching the toes of the normal leg caused the opposite deafferented leg to be promptly thrust out in extension. In most cases the cat, though fully awake, could not inhibit this reflex, and the limb remained in full extension as long as the stimulus was applied. The response was steady and persistent, and appeared to outlive the stimulus by an appreciable period. It imposed on the limb a definite posture and appeared to be as definitely tonic as are the labyrinthine and neck reflexes described by Magnus. It seemed desirable, therefore, to obtain tracings of these reflexes in decerebrate animals.

In describing the crossed extensor reflex in the decerebrate cat, Sherrington [24] said: "The reflex contraction thus excited in the vasto-crureus when that muscle has its own afferents intact is of considerable duration; the contraction rises deliberately to a maximum, which is maintained for some seconds and then slowly declines. But in the deafferented preparation the course of the reflex contraction runs otherwise. It rushes to its maximum and then as quickly or almost as quickly subsides, presenting hardly a trace of the prolonged maintenance and slow decline characteristic of it in the decerebrate muscle still possessing afferents."

In cats decerebrated at the upper border of the mesencephalon, we [34] have been able to confirm these observations of Sherrington. Under these conditions the crossed extensor reflex in normal muscle is maintained long after the stimulus ends, but in deafferented muscle it

33. Pollock, L. J.: Muscle Tone, J. A. M. A. **91**:222 (July 28) 1928.
34. Ranson, S. W., and Hinsey, J. C.: Am. J. Physiol. **88**:52, 1929.

ceases abruptly on the cessation of the stimulus. If, however, the transection of the brain stem is made at the upper border of the pons, there is little, if any, difference in the crossed extensor reflex as obtained from normal and deafferented muscle. After such low decerebrations typical tonic crossed extensor reflexes can be obtained easily from muscles the hypothetic parasympathetic tonus fibers of which have been cut in the dorsal roots. It seems probable that after high decerebrations a tone inhibitory center located in the upper part of the mesencephalon is responsible for the rapid relaxations of the crossed extensor reflexes obtained from deafferented muscles. When this center has been cut away in a low decerebration, the crossed extensor reflex has essentially the same tonic character whether or not the muscle is deafferented.

Labyrinthine Reflexes.—Spiegel [35] found that section of the dorsal root did not prevent the development of postural labyrinthine reflexes in the frog. I [25] have found that tonic neck and labyrinthine reflexes, expressed as flexion or extension of the hind legs and obtained by rotating the head first to one side and then to the other or by raising or lowering the head, were easily obtained in six of eight decerebrated cats and were, without exception, brisker on the deafferented than on the control side. In the cat, Pollock [33] found, in experiments which were conducted in collaboration with Davis, that section of the posterior roots in a decerebrate cat does not sufficiently modify the rigidity produced by labyrinthine reflexes to enable one to point out the differences between such rigidity and that in an animal with the posterior roots intact. This makes it clear that the integrity of the hypothetic parasympathetic fibers in the dorsal roots is not essential for the development of labyrinthine tonic reflexes.

Tetanus.—This is another condition in which there is a marked exaggeration of the tonus of the extensor muscles. Liljestrand and Magnus [30] thought that section of the dorsal root prevented the development of tetanus rigidity. Elsewhere, I [36] have reviewed the literature on this subject in some detail and have recorded experiments which show that, while under certain conditions the experiments of Liljestrand and Magnus can be repeated with similar results, it is not true that section of the dorsal roots prevents the development of tetanus rigidity. The onset of the rigidity, as measured by the resistance to passive movement, may be delayed by section of the dorsal roots. But tetanus rigidity and even contracture develops in deafferented muscle. Rigidity and contracture develop even after degeneration of all of the sensory

35. Spiegel, E. A.: Zur Physiologie und Pathologie des Skelettmuskeltonus, Berlin, Gustav Fischer, 1923.

36. Ranson, S. W.: Local Tetanus: Study of Muscle Tonus and Contracture, Arch. Neurol. & Psychiat. **20**:663 (Oct.) 1928.

fibers has been brought about by removal of the spinal ganglia. This rules out the possibility that the rigidity might be due to the action of the toxin on the spinal ganglion cells and on the fibers arising from them and ending in the muscles. But it must be admitted that there is some evidence for a direct action of the toxin on the muscle fibers.

Experiments with Nicotine.—Some years ago, I [37] presented evidence in favor of Frank's hypothesis. In decerebrate cats the roots and spinal ganglia of one lumbosacral plexus were exposed and, without opening the dura, were bathed in a solution of 0.04 per cent nicotine. This caused a marked decrease in the rigidity without decreasing the extent of the crossed extensor reflex obtained in either leg by pinching the toes of the opposite foot. In fact, this reflex was even brisker on the nicotinized side. This showed that the conductivity in the motor and sensory fibers was not noticeably impaired. The only explanation of these results which occurred to me at that time was that the nicotine acted on the spinal ganglia, blocking synapses over which the tonic impulses from the dorsal roots had to pass in order to traverse the spinal ganglia. Another explanation of these results has been suggested to me by Forbes.[38] Forbes and Olmsted [39] have presented evidence to show that in tonic contractions, such as the crossed extensor reflex, nerve impulses travel down the motor fibers in such rapid succession that the fibers are in a relatively refractory state, and a considerable percentage of the motor nerve impulses, and probably a majority of them, are subnormal. These subnormal impulses are more readily stopped at an alcohol block in the nerve that are normal full-sized impulses. It is possible that nicotine produces a similar block in the nerve interrupting these rapidly repeated subnormal impulses but allowing the full-sized impulses to pass.

Stimulation of the Dorsal Roots.—The question of the parasympathetic tonus fibers in the dorsal roots may be approached in another way. These fibers, if present in the dorsal roots, must also be present in the peripheral nerves and should be brought into play when a motor nerve is stimulated. A single induction shock applied to a motor nerve, however, causes only a brief twitch. To produce the pseudomotor phenomenon, Hinsey and Gasser [6] had to apply strong and rapidly repeated stimuli to the sensory fibers remaining in the sciatic nerve after degenerative section of the ventral roots. If the same small fibers with high threshold that produce the pseudomotor phenomenon are concerned with tonus, they could be activated only by strong rapidly repeated stimuli. When a peripheral nerve like the popliteal is stim-

37. Ranson, S. W.: J. Comp. Neurol. **40**:1, 1926.
38. Forbes, A.: Personal communication to the author.
39. Forbes, A., and Olmsted, J. M. D.: Am. J. Physiol. **73**:17, 1925.

ulated with strong rapidly repeated induction shocks for a period as long as the latency of the pseudomotor phenomenon, the resulting tetanus of the gastrocnemius goes over into a contracture which relaxes slowly. This is what physiologists call a fatigue contracture. On the assumption that such a fatigue contracture might be due to the activation of parasympathetic tonus fibers in the mixed nerve, I [40] applied similar stimuli to the seventh lumbar and first sacral ventral roots and recorded the contractions of the gastrocnemius. Prolonged stimulation of the ventral roots with strong faradic stimuli caused contracture in the gastrocnemius as readily as if the same stimuli had been applied to the mixed nerve. While no one has yet given a satisfactory explanation of this so-called fatigue contracture, it cannot be attributed to the stimulation of parasympathetic tonus fibers of dorsal root origin.

At the Oxford meeting of the British Association for the Advancement of Science, Denny-Brown [41] presented the mechanical and electrical records which he had made with the precise recording apparatus in use in the physiologic laboratory of Oxford University. He had been unable to find any difference in the records when the ventral roots alone were stimulated and when the stimulation was applied to the mixed nerve. This was advanced as evidence against the existence in the nerve of special tonus fibers derived from either the dorsal roots or the sympathetic.

HISTOLOGIC EVIDENCE

Endings of Dorsal Root Fibers in Muscle.—The idea that impulses, carried antidromically over parasympathetic fibers in the dorsal roots, are responsible for tonus at once raises the question as to what fibers of dorsal root origin actually end in muscles. If muscle possesses a double or as Ken Kuré [42] maintained a triple, innervation, this should be susceptible of histologic demonstration. Somatic motor fibers ending in motor end-plates are easy to find, but the case is otherwise in regard to the hypothetic sympathetic and parasympathetic endings. Others will consider the vexed question of the sympathetic innervation of skeletal muscle. One must inquire, however, whether or not parasympathetic fibers of dorsal root origin can be demonstrated ending on skeletal muscle fibers.

One can scarcely conceive of tonic impulses being conveyed antidromically over the sensory fibers which end in the muscle spindles, because the muscle spindles are not sufficiently numerous to account for

40. Unpublished data.

41. Denny-Brown, D.: Unpublished paper.

42. Kuré, K.; Shinosaki, T., and Shinagawa, F.: Ztschr. f. d. ges. exper. Med. **46**:144, 1925.

powerful tonic contractions or for the high tension developed by the gastrocnemius in the pseudomotor phenomenon. Other muscle fibers must be involved. In addition to the spindles there are in skeletal muscles three other kinds of sensory end-organs—tendon spindles, pacinian corpuscles and free nerve endings—all of which, since they are found in the connective tissue framework and not directly on the muscle fibers, may be excluded as possible factors in the antidromic conduction of tonic impulses. At one time I was inclined to consider the possibility that other fibers of dorsal root origin might end on muscle fibers. Boeke [43] had apparently demonstrated the double innervation of skeletal muscle fibers; and there were some reasons for thinking that the fine unmyelinated fibers, which he thought were sympathetic, were really of dorsal root origin, perhaps branches of the large fibers to the muscle spindles and tendon spindles. Kulchitsky's [44] studies of frogs' muscle stained with methylene blue (methylthionine chloride, U. S. P.) offered some justification for such an interpretation. He demonstrated that there are unmyelinated fibers in frog muscle which are branches of myelinated sensory fibers. These fine fibers end "in a bush of ramifying threads with leaf-like expansions at their ends." These endings rest directly on the surface of the muscle. They are epilemmal and possess no granular sole-plate nor nuclei. They correspond to the grapelike sensory endings found in the extrinsic muscles of the mammalian eye by Huber,[45] Crevatin [46] and Dogiel.[47] In order to rule out the possibility that the unmyelinated fibers, which Boeke and Dusser de Barenne,[48] Agduhr [49] and Kuntz and Kerper [50] found innervating mammalian skeletal muscle, were really of dorsal root origin, Hinsey began at my suggestion a thoroughgoing investigation of the innervation of the quadriceps muscle of the cat. He isolated in turn the motor, sensory and sympathetic fibers supplying the muscle. The sensory fibers were isolated by degenerative section of the ventral roots and removal of the lumbar sympathetic chain. The sympathetic fibers were isolated by cutting the nerves distal to the spinal ganglia and proximal to the rami communicantes. The material was stained by the pyridine silver technic, the adequacy of which was shown by the wealth

43. Boeke, J.: Brain **44**:1, 1921.

44. Kulchitsky, N.: J. Anat. **59**:1, 1924.

45. Huber, G. C.: Anat. Anz. **15**:335, 1899.

46. Crevatin, F.: Rendic. r. Accad. d. sc. d. Ist. di Bologna **5**:37, 1900.

47. Dogiel, A. S.: Arch. f. mikr. Anat. **68**:501, 1906.

48. Boeke, J., and Dusser de Barenne, J. G.: Koninkl. Akad. v. Wetensch., Amsterdam **21**:1227, 1919.

49. Agduhr, E.: Verhandel. d. k. Akad. v. Wetensch. **20**:1, 1919.

50. Kuntz, A., and Kerper, A. H.: Proc. Soc. Exper. Biol. & Med. **22**:23, 1924.

of fine fibers which it stained on the intramuscular blood vessels. Hinsey [9] was unable to demonstrate Boeke's accessory fibers, and could find no evidence of any fibers of dorsal root origin ending in the muscle except those which terminated in muscle spindles, tendon spindles, pacinian corpuscles and free nerve endings in the connective tissue. Some of these free sensory nerve endings lay close to muscle fibers, but the number of such close approximations was so small that it is not possible to attach any functional significance to them.

Hinsey [51] also made a study of the innervation of the blood vessels in these preparations in which the sensory and sympathetic fibers had been isolated. Fibers of dorsal root origin were observed in the adventitia of the small arteries and veins, arterioles and venules. While extending to the terminal arterioles, they were not found on the capillaries. Hinsey gave a detailed survey of the literature on the innervation of muscle and blood vessels. His work makes it clear that if antidromic impulses, conveyed over the dorsal roots, exert an influence on tonus it can be only by way of the blood vessels. How this might come about has already been suggested in the first part of this paper.

Efferent Fibers in the Dorsal Roots.—It is well known that there are efferent fibers in the dorsal roots of birds (Cajal,[52] Lenhossék [53] and van Gehuchten [54]), but their presence in mammals has never been satisfactorily demonstrated. I may pass over the older work of Joseph,[55] and Singer and Münzer [56] to consider the recent paper of Ken Kuré and his associates.[57] From nine to twelve weeks after section of the dorsal roots proximal to the spinal ganglia, Ken Kuré found many fine myelinated fibers in the central stumps of the divided roots. These were interpreted as parasympathetic fibers arising from cells in the posterior horn and ending in the spinal ganglia in synaptic relation with neurons the fibers of which run out in the peripheral nerves. After section of the dorsal roots, they found chromatolysis of cells in the base of the posterior horn. Chromatolysis of cells in the gray matter of the spinal cord as a result of section of the dorsal roots

51. Hinsey, J. C.: J. Comp. Neurol. **47**:23, 1928.

52. Cajal, S. Ramón y: Pequeñas communicaciones anatomicas, Barcelona, 1890.

53. Von Lenhossék, M.: Anat. Anz. **5**:360, 1890.

54. Van Gehuchten, A.: Anat. Anz. **8**:215, 1893.

55. Joseph, M.: Arch. f. Anat. u. Physiol., 1887, p. 296.

56. Singer, J., and Münzer, E.: Denkschr. d. k. Akad. d. Wissensch. Math-naturw. Klasse, Wien, 1895, vol. 57.

57. Kuré, K.; Nitta, Y.; Tsuji, M.; Shiraishi, K., and Suenaga, B.: Pflüger's Arch. f. d. ges. Physiol. **218**:573, 1928.

has been seen by other observers—Warrington [58] and Lapinsky [59]—but it is possible that this is due to vascular disturbances resulting from section of the small arteries accompanying the roots. Ken Kuré's observation of myelinated fibers in the proximal stumps of the severed roots many weeks after the section cannot be considered as evidence because of the possibility of regeneration from the spinal ganglia which were left in place.

Timasheff [60] cut lumbar dorsal roots in dogs, and after the lapse of from three to fifteen days studied the part of the roots still attached to the spinal ganglia in preparations stained by the Marchi and other methods. He found that about 5 per cent of the fibers underwent degeneration. There was chromatolysis in some of the cells of the corresponding segments of the spinal cord chiefly in the gray matter of the same but also to some extent in that of the opposite side. Cells in all parts of the gray matter were involved, but chiefly in the anterior

Experiments on the Stumps of Divided Dorsal Roots

Number	Roots	Operation	Duration, Days	Stain
1	L 6, 7, S 1	Ligated	24	Pyridine silver
2	L 4, 5, 6	Ligated	24	Pyridine silver
3	L 6, 7	Ligated	74	Pal-Weigert
4	L 5, 6, 7	Cut	74	Pyridine silver
5	L 6, 7	Cut	24	Marchi
6	L 7, S 1	Cut	70	Pyridine silver
7	L 7, S 1	Cut	54	Pal-Weigert
8	L 6, 7	Cut	20	Marchi
9	L 6, 7	Cut	14	Marchi
10	L 6, 7	Cut	51	Pyridine silver

and lateral parts of the anterior gray column. He concluded that there were a few centrifugal fibers in the dorsal roots. The evidence however, is far from convincing.

In the course of other studies I [61] had the opportunity to examine the proximal stumps of divided dorsal roots stained with Pal-Weigert, Marchi and pyridine silver. In none of these have I ever seen any clearcut evidence of efferent dorsal root fibers. The experiments are listed in the accompanying table. In the first four of these experiments the lumbosacral dorsal roots were ligated proximal to the spinal ganglia, in the remaining six they were cut. So far as could be determined from the Marchi preparations, the fibers in the proximal stumps underwent degeneration. Obviously this does not exclude the possibility that fine myelinated or unmyelinated fibers may have remained normal and passed unnoticed in the Marchi preparations.

58. Warrington, W. B.: J. Physiol. **23**:112, 1898-1899.
59. Lapinsky, M.: Arch. f. Psychiat. **42**:869, 1907.
60. Timasheff, N. K.: Nevrol. Vestnik **18**:777, 1911.
61. Ranson, S. W.: J. Comp. Neurol. **24**:531, 1914.

In the pyridine silver preparations of cats 1, 2, 4, 6 and 10 a varying small number of fine axons of normal appearance were seen entering the cord from the degenerated root. Also in cats 3 and 7 a few fine myelinated fibers could be seen in degenerated roots as they entered the cord. These fibers may have been efferent dorsal root fibers the cell bodies of which were within the cord, or they may have been regenerating fibers growing from the root into the cord. The spinal ganglia had not been removed, and the time which had elapsed was sufficient for the appearance of regenerating fibers (twenty-four days for unmyelinated fibers and fifty-four days for myelinated fibers). The fibers were more abundant near the cut end of the root and increased in number with the time which the animals survived the operation.

In cats 1 and 2, twenty-four days after the roots had been tied, there were a moderate number of fine axons in the dorsal roots. These were more abundant near the cut end of the root than next the cord. They differed from the normal unmyelinated fibers chiefly in their irregular course and grouping. Some were branched, but end-bulbs, typical of regenerating fibers, were not seen. As has been said, only a few axons could be traced from the root into the cord. In cat 4, seventy-four days after the operation, the proximal stumps of the divided dorsal roots were crowded with fine axons which resembled normal fibers. These were present in great numbers up to the point where neuroglia takes the place of connective tissue just before the root enters the cord. Beyond this point only a few axons extended into the cord. Similar observations were made on Weigert preparations from cats 6 and 10.

There can be no question but that the great number of fibers in the degenerated roots can be explained only on the basis of regeneration. Nevertheless, the possibility cannot be excluded that the fine fibers seen actually entering the cord may have had their cells of origin in the cord. It is to be regretted that the spinal ganglia were not removed in these experiments so as to exclude the possibility of regeneration. Only by excluding this possibility can the question of efferent dorsal root fibers be settled.

SUMMARY

A review is given of the facts which bear on Frank's hypothesis that tonic impulses are conveyed to the muscles antidromically over parasympathetic fibers in the dorsal roots.

The pseudomotor phenomenon, caused by stimulating the sensory fibers after the motor fibers to a muscle have degenerated, has much in common with the contracture caused in the same denervated muscle by acetylcholine, which is a parasympathetic drug with a powerful vasodilator action. The relation of these phenomena to antidromic vaso-

dilation is discussed. Antidromic vasodilation and the pseudomotor phenomenon are probably both brought about by the fine dorsal root fibers that accompany the blood vessels. Although the pseudomotor phenomenon and acetylcholine contracture are inhibited by epinephrine, they are not inhibited by large doses of scopolamine and atropine. Hence the pharmacologic evidence is against the reactions falling definitely in the parasympathetic class. On the other hand, the favorable action of atropine and scopolamine on the parkinsonian rigidities must not be forgotten.

The importance of the dorsal roots for muscle tonus has been overstated. Contrary to the usual belief, deafferented muscle does not remain permanently atonic, but recovers some of its tone and may for a time become hypertonic. Decerebrate rigidity, tonic crossed extensor reflexes and labyrinthine tonic reflexes can be obtained from deafferented muscle. This shows that whatever rôle the dorsal roots may play in tonus, the fibers of the ventral roots are sufficient in themselves to produce tonic contractions.

No one has as yet succeeded in showing that stimulation of the dorsal root fibers concomitantly with the motor fibers alters the character of the contraction evoked by stimulation of the ventral root fibers alone.

There is no histologic evidence that dorsal root fibers have any endings on the muscle fibers in the limbs of mammals other than the endings in the muscle spindles. Tendon spindles, pacinian corpuscles and free nerve endings are found in the intramuscular connective tissue and cannot come into consideration in this connection. The branches of sensory fibers, which end in grapelike terminals on the surface of frog muscle fibers and in the intrinsic muscles of the mammalian eye, appear to be absent from the limb muscles of mammals. A histologic demonstration of parasympathetic nerve endings in the mammalian limb muscles has not yet been given.

It remains an open question whether or not there are any efferent fibers in the dorsal roots; even if these are absent the possibility of antidromic conduction over the sensory fibers, as postulated by Langley for vasodilation, remains.

THE SYMPATHETIC DIVISION OF THE AUTONOMIC SYSTEM IN RELATION TO HOMEOSTASIS*

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The living parts of complex organisms, such as human beings are, do not come into direct contact with the surrounding air. They are separated from the air by a layer of mucus or by a layer of dead horny skin. The actually living parts are embedded in the fluids which bathe the cells—the blood or the lymph. These fluids, as Claude Bernard [1] pointed out half a century ago, constitute the "milieu interne" or the internal environment. This internal environment, or, as it may be called, the "fluid matrix," of the living structures is a product of the organism itself, developing as the organism develops. Furthermore, it is controlled by the organism. As in the course of evolution organisms have become more perfect, it is noteworthy that they have become gradually more free from changes in the external environment; more free, for example, from changes of humidity, changes of temperature and variations of oxygen tension. This achievement of freedom from disturbance, in spite of extensive changes in the outer world, has been brought about by mechanisms which maintain uniformity of the fluid matrix. Claude Bernard clearly recognized this fact when he stated that "it is the fixity of the 'milieu intérieur' which is the condition of free and independent life." He further declared that "all the vital mechanisms, however varied they may be, have only one object—that of preserving constant the conditions of life in the internal environment."

One might speak of the steady states which are maintained in the fluid matrix of the body as equilibria. Thus one would have the equilibrium of temperature, the equilibrium of sugar in the blood and the equilibrium of the oxygen tension in the tissues. The term equilibrium, however, as used by physicists, chemists and physical-chemists has come to have a fairly exact meaning in relation to physicochemical processes. There are, of course, such processes in the body, but many of the steady states, as illustrated by the cases just cited, are dependent on "reactions" which are peculiar to the organization of living beings. These reactions are much more complex and indirect than the ordinary physical and

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1. Bernard, Claude: Leçons sur les phénomènes de la vie, Paris, J. B. Baillière et fils, 1879, p. 5.

chemical adjustments, i.e., they are peculiarly physiologic. Under these circumstances it has seemed to me that a special designation is desirable. Accordingly, I [2] have suggested that the general idea of uniformity or stability in the organism be called "homeostasis," [3] a term the meaning of which is clear and the other forms of which, as in the adjective "homeostatic" and in the generic term "homeostatics," are likewise clear and descriptive.

The great importance of homeostasis is well illustrated in what occurs when agencies which maintain it are lacking. The frog, so commonly used in the physiologic laboratory, has no temperature regulating apparatus. The only way in which the animal can survive the cold northern winter is by sinking to the bottom of a pool when cold weather comes and living in the mud during the winter months. The animal likewise has no means for maintaining its water content, and if left in the dry air of the laboratory for a day or two, it becomes as desiccated as a mummy. Higher forms, such as the birds and mammals, have developed reactions for protection against such dangers. They have arrangements for maintaining a fairly constant temperature and for preserving the water content of the body, and devices also for stabilizing other highly important conditions for the cellular functions.

I can best approach the rôle which the vegetative nervous system plays in the regulation of homeostasis by calling attention to the different rôles which the voluntary and the involuntary nervous systems play. The voluntary nervous system, or, to use physiologic terms, the cerebrospinal nervous system, is connected with receptors on the body surface and with effectors in the skeletal muscles which operate the bony lever systems of the body. It is through this system that the human being becomes acquainted with the vast ranges of his environment, from the object which touches him to the remotest star, incredible light-years distant from him; and it is through this system that he causes all the extraordinary changes in his surroundings, from building skyscrapers, airplanes and ocean liners to turning on the radio. This system, by means of which one learns of one's surroundings and acts and reacts on them, may be thought of as the "exterofective system." Every response of this system, even the slightest, is associated with the using up

2. Cannon, W. B.: Physiological Regulation of Normal States: Some Tentative Postulates Concerning Biological Homeostatics, Jubilee Volume for Charles Richet, Paris, 1926, p. 91.

3. The use of the word "homeostasis" has been criticized as implying a fixed and stagnant state. "Stasis" means that, but also means condition. "Homeo," the abbreviated form of 'homoio," is prefixed instead of "homo," because the former indicates like or similar, whereas the latter, meaning the same, indicates rigidity. The term "homeokinesis" already has a place in biologic nomenclature in a relation distinct from that here described; and even if available would hardly be appropriate to define, for example, the blood sugar level.

of oxygen and energy-yielding material, and at the same time with the production of waste. Consequently, the activities of the exterofective system are continuously producing changes in the fluid matrix of the body. In order that the internal environment shall be maintained in a uniform state, external activity must necessarily be mirrored in an internal adjustment. I wish to bring evidence that the system which manages these internal adjustments is, in the main, the sympathetic division of the autonomic system. One may regard the autonomic system which innervates smooth muscle (and, incidentally, cardiac muscle) and glands, as an "interofective system," [4] managing the internal affairs of the body. And of the autonomic system the sympathetic division is especially concerned with keeping the organs fit for action. It mobilizes the bodily forces, and is a stabilizing agency when homeostasis is threatened. The functioning of the sympathetic division as an agency of homeostasis can be made clear by illustrations.

THE FUNCTIONING OF THE SYMPATHETIC DIVISION

I will next consider the changes which are brought about by vigorous muscular effort—the sort of activity of the exterofective system that is evoked by strong and repeated stimulation.

1. The activity of muscles is associated with the using up of sugar. Indeed, continuous muscular activity will considerably reduce the sugar in the blood. We [5] have recently shown that after two hours in a treadmill the average level of blood sugar in dogs falls from about 90 to about 66 mg. per hundred cubic centimeters of blood. That this fall occurs in spite of a constant renewal from the liver is proved by the fact that continuous prolonged exercise will deplete the liver of its store of glycogen.[6] If the liver is extirpated the ordinary functioning of the body soon reduces the blood sugar to a point at which convulsions and coma lead on to death.[7] An overdose of insulin brings about similar dire results unless the blood sugar is increased in amount.[8] It is obvious,

4. "Interofective," corresponding to interoceptive, is employed to refer to the internal organs; "propriofective" has been suggested, but that term, by analogy with proprioceptive, would properly indicate action on only the deep body tissues.

5. Campos, F. A. de M.; Cannon, W. B.; Lundin, H., and Walker, T. T.: Some Conditions Affecting the Capacity for Prolonged Muscular Work, Am. J. Physiol. **87**:680, 1929.

6. Külz, E.: Ueber den Einfluss angestrengter Körperbewegung auf den Glycogengehalt der Leber, Arch. f. d. ges. Physiol. **24**:41, 1880.

7. Mann, F. C., and Magath, T. B.: The Effect of Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73 (July) 1922.

8. Banting, F. G.; Best, C. H.; Collip, J. B.; Macleod, J. J. R., and Noble, E. C.: The Effect of Pancreatic Extract (Insulin) on Normal Rabbits, Am. J. Physiol. **62**:162, 1922.

therefore, that lowering of the glycemic level may cause serious danger. The arrangement whereby danger is avoided is operated by the sympathico-adrenal apparatus. As was shown by McIver, Bliss and me [9] some years ago, a reduction of the blood sugar to a point between 70 and 80 mg. per hundred cubic centimeters is associated with the stimulation of the sympathico-adrenal system. We used the denervated heart, which is extremely sensitive to an increase of epinephrine in the circulating blood, to indicate (by a faster beat) an increased adrenal secretion (chart 1). The lower the sugar level falls below 70 mg. per hundred cubic centimeters, the greater the activity of the sympathico-adrenal apparatus, and if the sugar percentage falls to the convulsive level the activity of the apparatus is maximal. Action of this apparatus liberates sugar from storage in the liver, and consequently the rapid drop of the glycemic percentage is checked (chart 1). If the agency (insulin, in our experiments) which is lowering the blood sugar is not overwhelmingly effective, the sympathico-adrenal apparatus liberates so much sugar from the liver that the danger is passed and the apparatus which has been called into activity subsides into inactivity. By artificial introduction of dextrose into the blood stream the protective service rendered by the sympathetic system and the adrenal medulla may be quickly dropped from a high degree of vigor to complete quiescence (chart 1). As we [10] showed in 1927, mere motion, such as walking a short distance across the floor, is accompanied by the bringing of the sympathico-adrenal system into service. It is clear that even slight activities of the exterofective system are accompanied by corresponding activities of the interofective system. Because of these associated activities, the sugar level is maintained above the dangerous region in spite of great demands for sugar from laboring muscles.

2. Vigorous muscular activity is associated with the development of heat. Indeed, under usual circumstances about 75 per cent of the energy of muscular contraction appears in the form of heat. If large muscle masses, like those found in both legs and both arms, are brought into supreme action in rapid repetition, as they are in a four mile rowing race, the amount of heat produced may be enormous. Unless the heat is dissipated, the temperature of the internal environment may rise to a serious degree. At rest a man of about 150 pounds (68 Kg.) uses about 250 cc. of oxygen per minute—enough to provide 1.25 calories, or enough, if he should lose no heat, to raise his body temperature about

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9. Cannon, W. B.; McIver, M., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924.

10. Cannon, W. B.; Britton, S. W.; Lewis, J. T., and Groeneveld, A.: The Influence of Motion and Emotion on Medulliadrenal Secretion, Am. J. Physiol. **79**:433, 1927.

1 C. in fifty minutes. The rate of oxygen intake during steady vigorous exercise may rise from 0.25 liter to 4.5 liters—an 18-fold increase. This would be enough to raise the body temperature, should there be no heat loss, as much as 6 C. (to 109 F.)—a dangerous rise—in about sixteen

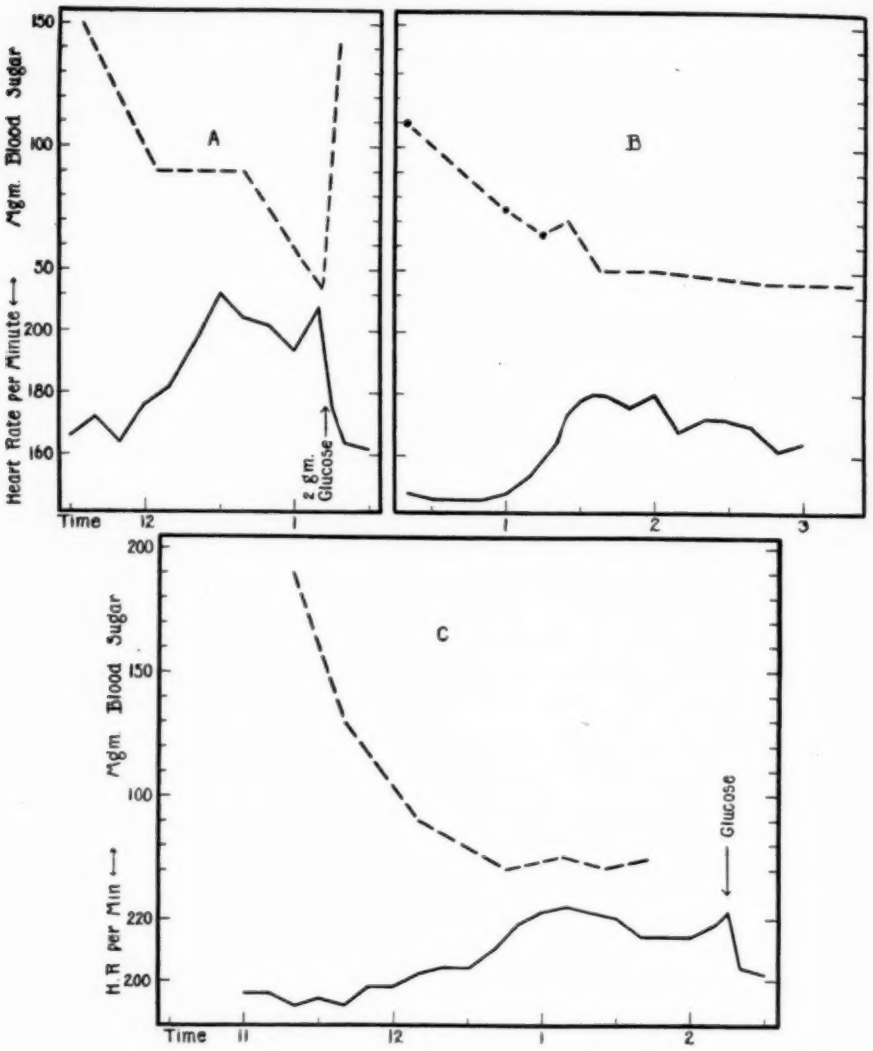

CHART 1.—Increase of rate of the denervated heart (solid line), in animals under chloralose anesthesia, when the falling blood sugar concentration (dash line) passed a critical point. In case *A*, the insulin was injected into the jugular vein at 11:33; in *B*, at 11:08, and in *C*, at 9:30. In each case 4 units per kilogram of body weight were injected.

minutes. As a matter of direct observation, temperatures of from 104 to 105 F. have been reported as consequent on exertion.[11] It is known that nerve cells of the brain will not endure temperatures higher than approximately 108 F. for several hours without undergoing irreversible chemical changes.[12] A high temperature of the fluid matrix of the body is, therefore, a matter of serious concern. When the blood temperature tends to rise, the sympathetic system is brought into action in two ways: —there is a relaxation of the peripheral blood vessels, the tone of which is governed by the sympathetic system, and a pouring out of sweat. The relaxation of the peripheral vessels allows a flushing of the skin with the hot blood, which may lose its heat to the exterior by convection and conduction if outer objects are cooler than the blood. The sweat which is liberated on the body surface evaporates if the air is not too humid, and by evaporation the extra heat which is being produced is carried away. Thus the tendency toward a rise of temperature is prevented by the interofective action of the sympathetic system.

In this connection it is pertinent to mention the rôle of the sympathetic system when there is an opposite tendency—i.e., when a cold environment rapidly removes heat from the body and there is a tendency toward a fall of temperature. Under these circumstances that system again is brought into action. The hairs and the feathers are erected on animals provided with these means of keeping the body warm. Thereby more of a poorly conducting medium, air, is enmeshed in the layers immediately around the body. Simultaneously there is a constriction of the surface vessels which lessens the dissipation of heat through the skin. And attendant on that, or perhaps slightly later, there is, as we [13] have shown, a liberation of epinephrine into the blood stream (chart 2). Epinephrine has the effect of accelerating the processes of combustion in the body so that there is a greater production of heat at this time when more heat is required to keep the temperature of the internal environment from falling. If, in spite of the processes which lead to the conservation of heat and to chemical production of extra heat that I have just mentioned, there is, nevertheless, a fall of temperature, another agency is brought into action (i.e., shivering) which results in a great increase in the output of heat because of muscular contraction. There is no evidence, however, that shivering is induced by sympathetic impulses.

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11. Hill, L., and Flack, M.: Observations on Body Temperature, Blood Pressure and Alveolar Tension of Athletes, J. Physiol. **36**:11, 1907-1908.

12. Halliburton, W. D.: Biochemistry of Muscle and Nerve, Philadelphia, P. Blakiston's Son & Company, 1904, p. 111.

13. Cannon, W. B.; Querido, A.; Britton, S. W., and Bright, E. M.: The Rôle of Adrenal Secretion in the Chemical Control of Body Temperature, Am. J. Physiol. **79**:466, 1927.

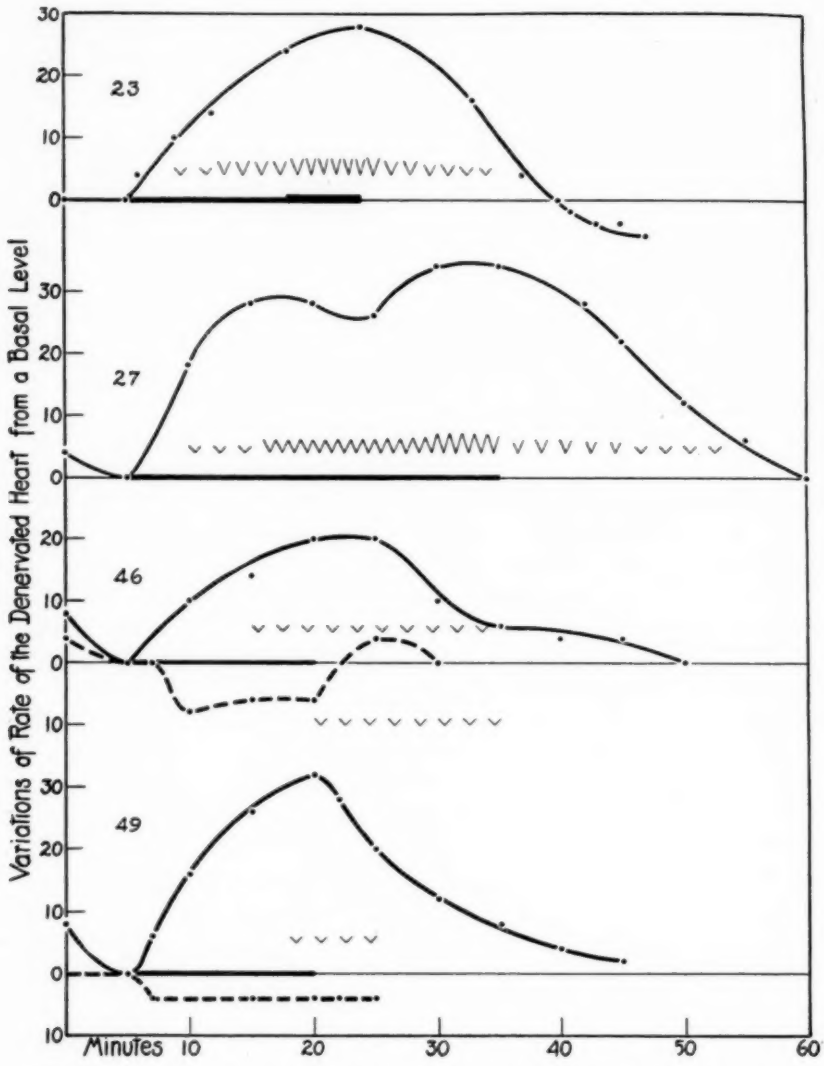

CHART 2.—Increases of rate of the denervated heart above a basal level when animals with adrenals intact (animals *23*, *27*, 46 and 49) were exposed to cold air. The period of exposure is denoted by a thickening of the base line; the double thickening in the case of animal *23* marks the time of a cold draught through an open door. Shivering is indicated by separate *v's* when it was intermittent, and by connected *v's* when it was continuous. The size of the *v's* marks roughly the intensity. The dash lines in cases 46 and 49 show the changes of heart rate under similar conditions of exposure after exclusion of the medulliadrenal secretion.

From the foregoing data it is evident that the homeostasis of the temperature of the internal environment is largely under control of organs and agencies which are dominated by the sympathetic division of the autonomic system.

3. When one engages in strenuous muscular work there is a tendency for the reaction of the blood to shift toward the acid side of neutrality. This is due to increase of carbonic and of lactic acid which are produced in consequence of the neuromuscular action. Again the change is not without danger. As is well known, in pathologic states a condition of acidosis may develop to such a degree that the functions of the nervous system are impaired, and, if they are not rectified, coma and death supervene. Long before any such stage as this is reached, as a consequence of muscular effort, respiratory movements greatly increase the ventilation of the lungs so that excess carbon dioxide liberated from the blood is carried away to the outer atmosphere. The muscles of respiration are, in the main, striated muscles and not under the control of the sympathetic system. There are other muscles, however—those which surround the bronchioles—which are of the smooth variety and which are subject to sympathetic control. It is known that when the sympathetic nerve supply to the bronchioles is stimulated or when their action is mimicked by means of epinephrine, the smooth muscles relax and the lumen of the bronchioles is thereby enlarged.[14] Thus, the tubular passageways are accommodated to the larger ventilation in vigorous effort, and the air moves to and fro with less friction. As previously mentioned, there is clear evidence that the sympathetic system is brought into action even when there is minor activity of the exterofective system. It seems highly probable, therefore, that whenever one engages in strenuous exertion there is a dilatation of the bronchioles, i.e., an exhibition of the functioning of the interofective system at a time when homeostasis of the acid-base relationship in the blood becomes important.

4. At the same time that there is a greater development of carbonic acid as a consequence of muscular work there is a greatly increased need of oxygen. Indeed, the demand for oxygen may be greater than can be supplied, although the blood flow through the contracting muscles may be increased as much as nine times and the oxygen consumption may be increased as much as eighteen times what it is during rest.[15] Under such circumstances the organism goes into an "oxygen debt" which must be paid later at a quiet time by the burning of accumulated waste.

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14. Jackson, D. E.: The Pulmonary Action of the Adrenal Glands, J. Pharmacol. & Exper. Therap. **4**:59, 1912.

15. Bainbridge, F. A.: The Physiology of Muscular Exercise, London, Longmans, Green & Company, 1923, p. 90.

The problem of providing an adequate oxygen supply for the tissues is met by a wider variety of devices than are invoked in meeting any other bodily need. The agencies of primary concern are the oxygen carriers, i.e., the red blood corpuscles. Under normal conditions they leave the lungs almost completely loaded; it is impossible, therefore, to increase the oxygen supply by increasing the individual load. The simplest mode of increasing the supply is by increasing in a given time the number of trips made by the corpuscles from the lungs to the needy organs. This end is achieved by driving the blood largely away from the splanchnic area (by splanchnic vasoconstriction) and by accelerating the heart beat. These two changes bring about an increase of arterial pressure which, during continued muscular effort, may be 50 mm. or more of mercury above the resting level.[16] In consequence of this higher head of pressure, blood flows faster, especially through such organs as the brain and spinal cord and the heart and the laboring muscles, in which the blood vessels either do not contract in the presence of a high general arterial pressure or are actually dilated. Because of these adjustments the total circulation rate may be augmented by as much as four times and the rate through the contracting muscles, where vessels are dilated, may be, as we have noted, much faster still. In addition to this faster rate there is a greater unloading of the oxygen in the active parts. For both reasons, therefore, a greatly augmented supply of oxygen is provided.

The organism not only can make more effective use of the available corpuscles by speeding up the circulation, but can also increase the number of available corpuscles in circulation. Recent evidence has shown that the spleen in the resting state of an animal may be three or more times as large as it is during activity or after death.[17] The pulp of the resting spleen contains corpuscles in a concentrated state—from 50 to 100 per cent more concentrated than in the circulating blood.[18] When there is need for oxygen, as in high altitudes, in carbon monoxide poisoning or during vigorous muscular exercise, the spleen promptly contracts and discharges its content into the general blood stream.[19] Thus within a few minutes after exertion has started, there may be an increase of the red corpuscles in circulation amounting to as high

16. Bowen, W. P.: Changes in the Heart Rate, Blood Pressure, and Duration of Systole Resulting from Bicycling, Am. J. Physiol. **11**:59, 1904.

17. Barcroft, J., and Stephens, J. G.: The Size of the Spleen, J. Physiol. **64**:1, 1927.

18. Scheunert, A., and Krzywanek, F. W.: Weitere Untersuchungen über Schwankungen der Blutkörperchenmenge, Arch. f. d. ges. Physiol. **213**:198, 1926.

19. Barcroft, J.: Die Stellung der Milz in Kreislaufsystem, Ergebn. d. Physiol. **25**:818, 1926.

as 25 per cent or more [20] (chart 3). These corpuscles, like those previously in currency, are sent through the vascular circuit at the greater speed resulting from the high arterial pressure. Their efficacy as carriers, therefore, is to be multiplied by the faster rate of flow which prevails.

In surveying this group of changes directed toward maintenance of a proper oxygen tension in the tissues, one notes that at every point the interofective service of the sympathetic division is at work. It causes constriction of the splanchnic vessels, it accelerates the heart and it

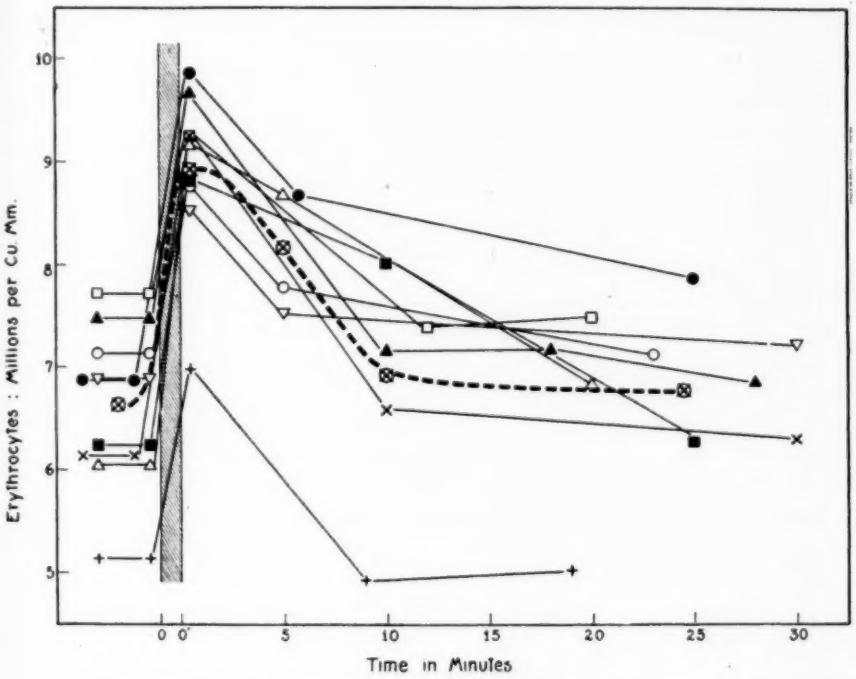

CHART 3.—The course of emotional polycythemia—a graphic record of nine cases. The vertical, shaded band represents the one minute period of emotional excitement; the thick dash line, the average of the nine cases.

brings about contraction of the spleen. Since the red blood corpuscles are instrumental not only in carrying oxygen from lungs to tissues but also in carrying carbon dioxide from tissues to lungs, these agencies which I have been considering in relation to oxygen are also effective in preventing the development of a harmful acid reaction in the laboring muscles. It is evident that the interofective service of the sympathetic

20. Cannon, W. B., and Izquierdo, J. J.: Emotional Polycythemia in Relation to Sympathetic and Medulliadrenal Action on the Spleen, Am. J. Physiol. **84**:545, 1928.

division plays a most important rôle with respect to the homeostasis of both the oxygen supply to the tissues and the acid-base relationship in the blood.

5. I have illustrated the rôle of the sympathetic division of the autonomic system as it operates during the performance of muscular work. It is a matter of interest that all the changes which I have mentioned—the liberation of sugar from the liver, the pouring out of sweat, the dilatation of the bronchioles, the contraction of the splanchnic area, the acceleration of the heart and the discharge of corpuscles from the spleen into the general circulation (chart 3)—occur also in emotional excitement.[20] As I [21] have already pointed out elsewhere, the association of these changes with such strong emotions as fear and rage lends strong support to the idea that emotional states are anticipatory of action, for every one of these changes renders the organism in which they occur more capable of supreme and prolonged struggle.

In 1914, I [22] called attention to a general division of functions between the cranial portion of the autonomic system and the thoracolumbar or sympathetic portion. The cranial portion appears to be conservative and upbuilding in its effects. The third nerve, for example, protects the retina against too bright light by constricting the pupil. The vagus holds the heart in check when there is no need for rapid beating; the seventh and ninth cranial nerves cause secretion of saliva favorable for the ingestion of food and digestion of starches in the stomach, and the tenth, the vagus, induces a flow of gastric and of pancreatic juice and establishes and maintains tone in the alimentary tract. Furthermore, through action on the pancreas the vagus, by liberating insulin, favors the storage of glycogen in the liver.[23] All these processes may be summed up as protective and conservative—the cranial autonomic system is concerned with establishing the bodily reserves. It is known from physiologic tests that when an organ is innervated by both the cranial and the sympathetic divisions of the autonomic system the effects of stimulation are, as a rule, opposed. For example, the vagi (of the cranial division) slow the heart, the accelerators (of the sympathetic division) make it beat faster; so, likewise, there is opposite action on the iris, the blood vessels of the salivary glands, the stomach and intestines and other structures. Since the sympathetic division is thus antagonistic to the cranial division, it is to be expected that when it is brought into action it will stop the con-

21. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed 2, New York, D. Appleton & Company, 1929.

22. Cannon, W. B.: The Interrelations of Emotions as Suggested by Recent Physiological Researches, Am. J. Psychol. **25**:256, 1914.

23. Britton, S. W.: The Nervous Control of Insulin Secretion, Am. J. Physiol. **74**:291, 1925.

servative, constructive processes of the cranial division. So it does. It temporarily abolishes the motions and secretion of the digestive organs; it greatly accelerates the heart; it widely dilates the pupils. In the main, when the sympathetic division induces these changes it also acts to mobilize the reserves which are needed for the proper and efficient functioning of the exterofective system and to maintain a steady state whenever the activities of the exterofective system tend to alter the homeostasis of the fluid matrix of the body.

One may consider total inactivity of the exterofective system as a basal state for the organism, i.e., a condition for minimal functioning of both the exterofective and the interofective systems. Whenever the exterofective system becomes active an internal disturbance is produced or tends to be produced, and associated therewith the basal interofective function is increased in order to maintain homeostasis.

It should be clear from the foregoing considerations that if the organism is maintained in a fairly constant basal condition, i.e., if there is not marked disturbance of the internal environment because of response to external stimuli, there is relatively little need for the functioning of the interofective system. This, in fact, has proved to be the case. We have been able to keep animals in the quiet circumstances of the laboratory for many months with the sympathetic system entirely removed from them. None of the adaptations which occur in the normal animal occur to a complete degree in these animals, and in some instances there is total failure of adjustment. It seems probable that although these animals can live normally in the sheltered conditions of the laboratory, they would not be able to make their way in the outer world.

Much of the work done at the Harvard Laboratories of Physiology for many years has been related to the general theory of the emergency function of the sympathico-adrenal system. When first conceived, the emergency theory was applied solely to situations which give rise to strong emotional states. The development of the idea that the sympathico-adrenal system is concerned with the maintenance of homeostasis, that it acts reciprocally with the exterofective system to prevent marked disturbances of the internal environment, is not a fundamental modification of the emergency theory. As already indicated, if emergencies do not arise—indeed, if reactions to the outer world do not occur—the sympathico-adrenal system is not a necessity. It plays its normal rôle, however, not only in emergencies of a grave character, but also in the minor adjustments of the organism required by responses to the environment.

SUMMARY

The doctrine expounded by Bernard, that the living parts of our bodies exist in an internal environment, or fluid matrix, is reviewed.

The importance of constancy (or homeostasis) of the matrix for continuous efficient action is emphasized.

The fact is pointed out that every response to a situation in the external environment is associated with disturbance in the internal environment. For constancy of the fluid matrix, therefore, every move in relation to the outer world must be attended by a rectifying process in the inner world of the organism.

Illustrations are given to show that the chief agency for the rectifying process is the sympathetic division of the autonomic system.

The cerebrospinal nervous system, responding to external stimuli, may be called the exterofective system, and the autonomic system, affecting the domestic affairs of the interior of the organism, may be called the interofective system.

When activity of the exterofective system disturbs the fluid matrix of the body it is the function of the sympathetic division to maintain homeostasis by its interofective functions.

It is pointed out that this concept does not contravene the theory of the emergency service of the sympathetic or sympathico-adrenal system; rather it is an extension of that theory from a restricted relation to major disturbances to a general relation to minor disturbances of the organism.

FUNCTIONAL SIGNIFICANCE OF HISTOLOGIC CHARACTER IN PREGANGLIONIC VISCERAL NEURONS*

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CINCINNATI

This article is based on a study of the distribution of various types of nerve cells throughout the human central nervous system, a study which has been continuous over a period of twenty years. A consideration of minute histologic differences in cell type has been carefully avoided, and only those differences have been taken into account which can be clearly demonstrated and which are not materially affected by variations in technic or in the condition of the tissues. The function of nerve cells, unlike that of nerve fibers, cannot be studied directly, but one can study the differences between nerve cells employed in different types of nervous reactions, and can note the constant histologic features of nerve cells which always occur in various nervous mechanisms the activities of which exhibit in common some well marked feature. In making such a comparison between the character of reactions and the character of the nerve cells employed, only clear and well known differences in nervous reactions have been used; for instance, it has been profitable to compare histologically various centers employed in reactions susceptible to fatigue with various centers engaged in reactions which show a marked resistance to fatigue. In studying the relation between some specific histologic feature of nerve cells and some specific feature of nervous reactions, the comparison should be made under varying conditions, with various combinations of all histologic and functional features other than the single pair which is being studied. Although this method of investigation is limited to those centers the exact connection of which are at present known, it has made possible a beginning in the study of the function of nerve cells.

THE RELATION OF FUNCTION TO THE SIZE, FORM AND INTERNAL STRUCTURE OF NEURONS

The function of a neuron presents two aspects. It may be considered to be the local activity which occurs within the limits of the neuron itself; this may be termed the immediate or intraneuronic function. The second aspect of function involves the neuron's connections, and

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this aspect of function offers two varieties; the structures to which neurons are connected may be grouped according to their topographic distribution or else according to their intrinsic function. The function of a neuron thus involves not only its immediate or intraneuronic activity, but also the neuron's topographic and specific functional relations to the entire organism. Every neuron type is a complex of histologic and functional characters, and any single character may occur in other types of neurons. The general functional significance of any specific histologic character may be determined by a study of all neuron types which exhibit the character in question, noting the features common to those reactions which employ such neuron types. Accordingly, any consideration of the functional significance of the histologic complex of preganglionic neurons must be based on the significance of the individual histologic characters of this neuron type, each one of these characters being studied in various types of neurons.

A neuron consists of two radically different portions, the cell body with its dendrites and the axon. The dendrites are merely extensions of the cytoplasm of the cell body, and should be distinguished from those processes which form the axis cylinders of sensory fibers in peripheral nerves. These peripheral sensory nerve fibers exhibit the fundamental characters of all axons, and their conduction toward the cell body depends exclusively on the fact that normally the stimulus must of necessity act at their peripheral ends. The difference in the location of the stimulus in sensory and motor peripheral nerve fibers is of great significance in relation to the entire organism, but it has no bearing on the intrinsic activity of the nerve fiber itself. While conduction can be directly studied in nerve fibers, it cannot be so studied within the other portion of the neuron, nor is there any ground for the assumption that within the dendrites and cell body conduction is of the same type as in nerve fibers. On this assumption has been based the erroneous conclusion that the peripheral type of conduction obtains throughout the entire extent of any single neuron, and that the special features of conduction within the central gray matter depend exclusively on the synapse. This incorrect conclusion is due partly to the lack of appreciation of the histologic relations which may exist between two nerve fibers. As the nervous impulse passes from the first nerve fiber (axon) to the second, the region of transition may exhibit any one of three histologic conditions. The two nerve fibers may be directly continuous, as in the typical peripheral sensory (unipolar) neurons, a condition which gains added significance from the fact that it is the result of the fusion of two originally separate nerve fibers (axons). The second type of relation between nerve fibers occurs in those bipolar neurons in which both processes are continued as nerve fibers, as in the peripheral vestibular

neurons; in this case, the two nerve fibers are separated by a cell body without any synapse. The third type is that in which the two nerve fibers belong to separate neurons and are separated not only by the cell body (and possibly dendrites) of the second neuron but also by a synapse. Every synapse is followed by the cell body of the second neuron, and since there is no proof that conduction is of the same type throughout the entire neuron, it follows that there is no basis for the assumption that only the synapse, and not also the cell body and dendrites, is responsible for the special features which characterize conduction within the central gray matter.

The study of various nervous mechanisms with reference to the size of the cell body which each mechanism employs reveals facts of interest. The size of the cell body with its dendrites is an indication of the extent of the neuron's activity, an indication of the frequency and duration of its stimulation; this involves the number of afferent connections and the extent to which these connections are employed. Neurons with large cell bodies are employed continuously, those with small cell bodies intermittently. Moreover, the size of the cell body is an indication of its capacity to resist fatigue; nervous fatigue of central origin is not a function of the synapse but of the cytoplasm of the cell body and dendrites. In reactions which are continuous and not subject to early fatigue, as the simpler proprioceptive reactions, not only the peripheral neurons but also the intermediate neurons have cell bodies and dendrites in which the volume of cytoplasm is large. In exteroceptive reactions, reactions of a more intermittent character and much more susceptible to fatigue, the cell bodies and dendrites of the intermediate neurons have much less cytoplasm. Nor can the resistance to nervous fatigue be explained on the basis of the use of neurons in rotation, for the small cell bodies of the exteroceptive reception centers are more numerous than the large cell bodies which constitute centers resistant to fatigue. Since the size of the cell body and dendrites is an indication of the neuron's resistance to fatigue, it must also be an indication of the tendency to maintain a uniform irritability. Neurons with large cell bodies are characteristic of centers employed in stable reactions, for the resistance to fatigue, the relatively uniform irritability and the relatively small numbers of cell bodies in such centers all tend to direct the nervous impulses into relatively fixed paths. On the other hand, neurons with small cell bodies characterize centers employed in labile reactions; the early fatigue, the variable irritability and the large number of cell bodies all tend to produce a labile type of reaction, one in which the pattern is readily modified.

While the size of the cell body is related to the immediate or intrinsic activity of the neuron, the form is related to its connections to other

structures. So far as the form of the cell body is of functional significance and not due merely to pressure, it is determined exclusively by the number, size and form of the neuron's processes. Through its processes every neuron is employed in the collection and distribution of nervous impulses. In afferent neurons the branching of the cell body processes is, as a rule, such as to result in the predominance of the diffusing activity of the entire neuron, while in the efferent neurons the collecting capacity, with rare exceptions, is greatly in excess of the diffusing capacity. In both the afferent and the efferent systems, long distance transmission involves a decrease in the number and an increase in the size of neurons. Owing to the increased size of the cell body, conduction is continuous and its speed is greater because of the increased diameter of the nerve fiber. Long distance transmission employs neurons the collecting capacity of which is increased in relation to the diffusing capacity; in long efferent paths the neurons have great integrative capacity, while in long afferent paths the diffusion characteristic of afferent neurons is reduced in the interest of efficient transmission (resistance to fatigue, uniform irritability, increased speed and economy of space occupied by the fiber tract).

Either the collecting or the diffusing cell body processes of the neuron may vary, not only in the number of connections, but also in the extent to which these connections differ topographically or functionally. Thus, the central fiber of the peripheral neuron of common sensation is widely distributed to the primary sensory reception centers, whereas the termination of the medial lemniscus is restricted in area. The efferent system presents many instructive examples of variation of neuron form as related to the number and type of connections effected by the dendrites. The Purkinje cells of the cerebellum possess great collecting capacity due to the profuse branching of the dendrites, but these dendrites supply one continuous territory; in other words, the collecting apparatus of the Purkinje cells is massive but of a low order of differentiation. In the inferior olives, the cell bodies receive impulses picked up within a narrow and almost continuous zone surrounding the cell body; in this case, the dendrites are numerous but small. Very different are the dendrites of the typical efferent neurons, such as the peripheral efferent neurons which supply skeletal muscle. In these neurons, each of the dendrites constitutes a separate collecting system the synapses of which are confined to a definite region relatively distant from the cell body, each dendrite system supplying a definite region which is separated from the regions supplied by the other dendrites of the same neuron. Owing to the separation of the fields of reception of each dendrite, the neuron receives impulses from many different sources, impulses from different levels of the nervous system and from nervous mechanisms of diverse

functions. These typical motor neurons possess an integrative capacity of a higher order than that of the Purkinje cells, although the actual number of synapses may be less. Accordingly, one must distinguish between the volume of impulses received by a neuron and the degree to which impulses arise from regions of the nervous system which are distinct; each of these two aspects of integration is, as just noted, related to a corresponding histologic character of the dendrites of the neuron.

The internal structure of the neuron permits of a histologic distinction between two functionally different portions, the axon which is resistant to fatigue and the cell body and dendrites which are subject to fatigue in inverse proportion to their volume. Moreover, the internal structure of the neuron may be related to function in the arrangement of the Nissl substance, this substance being arranged according to the integrative capacity of the neuron. A diffuse distribution is characteristic of afferent neurons, while in efferent neurons increasing integrating capacity is accompanied by a concentration of the Nissl substance into granules of increasing discreteness. The sharply defined, discrete character of the granules is related less to the volume of impulses received than it is to the capacity to integrate impulses from many diverse sources.

The foregoing discussion of the relation of function to the size, form and internal structure of neurons makes it possible to consider intelligently the functional significance of the complex of histologic characters presented by preganglionic visceral neurons. The latter problem becomes relatively simple and may be disposed of briefly.

THE FUNCTIONAL SIGNIFICANCE OF THE COMPLEX OF HISTOLOGIC CHARACTERS PRESENTED BY PREGANGLIONIC VISCERAL NEURONS

Histologically, as well as functionally, these neurons are efferent, but they resemble the more remote or premotor neurons rather than the peripheral somatic motor type. The latter, the typical motor neurons, constitute a well defined group, differences being limited to the size and to the number of impulses received, whereas the form and internal structure remain relatively constant as does the variety of source of the impulses received. The premotor neurons exhibit great differences in integrative capacity, the members differing not only in the size of the cell body but also in its internal structure and in the nature of its dendrites. The cell bodies and dendrites of some premotor neurons cannot with certainty be distinguished from those of neurons supplying skeletal muscle, but it is the less highly specialized premotor neurons which resemble the preganglionic neurons. Of all preganglionic neurons, those whose cell bodies constitute a portion of the dorsal vagus nucleus make the closest approach to the histologic type of neuron which supplies skeletal muscle; this resemblance is by no means perfect. These cell

bodies give rise to efferent vagus fibers which probably supply the heart, and they are of a histologic type intermediate between that of typical preganglionic neurons and of typical motor neurons which directly supply skeletal muscle. When these more highly specialized visceral neurons are compared with the typical motor neurons, it appears that the cell body is smaller and the dendrites are less numerous, shorter and of decreased diameter, while the concentration of the Nissl substance into sharply circumscribed granules is less pronounced. The dendrites of these preganglionic neurons are sufficiently numerous and of sufficient diameter and length to give to the cell body a form which is still definitely polygonal. Comparison of these highly specialized visceral neurons with the usual type of preganglionic neuron reveals that the latter have smaller cell bodies, that their dendrites are fewer, shorter and less massive, and that the cell body has a less marked polygonal form. While the Nissl substance of the typical preganglionic neurons still has the general arrangement of all efferent neurons it is by no means characteristic, since the granules are relatively poorly circumscribed. If one compares the dendrites of peripheral somatic efferent neurons, the dendrites of the large cell bodies in the dorsal vagus nucleus, and finally those of typical preganglionic cell bodies, one finds that arranged in this order the dendrites diminish in number, diameter and length. As a consequence the neurons, taken in this order, receive stimuli which decrease in number and in variety of distinct sources; in other words, there is a progressive decrease in the integrative capacity of the neuron.

The preganglionic visceral neurons do not form a distinct group differing fundamentally from neurons of the somatic efferent system. The separation of the nervous system into visceral and somatic systems is incomplete, for both visceral and somatic responses may follow stimuli received from either system; this separation is of necessity incomplete since otherwise it would be impossible to integrate all the activities of the organism. The preganglionic visceral neurons must be grouped under the efferent neurons, their general histologic character depending not on their inclusion within the visceral system but on the fact that these neurons are efferent or integrating. Their specific histologic characteristics depend on the extent of the demands for integration to which these neurons are subjected, and histologically their cell bodies cannot be distinguished from those of somatic premotor neurons of corresponding integrating capacity. The cell bodies of such premotor neurons occur, for instance, scattered throughout the exteroceptive reception centers and also grouped to form reflex centers along the central cochlear pathway. Such premotor neurons are employed only in very simple types of reactions, and histologically they indicate that they are subjected, with reference to integration, to relatively simple conditions.

CONCLUSIONS

The principal conclusions to be drawn from this article may be summed up as follows: The preganglionic visceral centers are merely reflex or coordinating centers of a low order. The histologic nature of these neurons does not depend fundamentally on the fact that they belong to the visceral system, but on the fact that visceral reactions are relatively simple. The same histologic character is shown by premotor neurons employed exclusively in somatic reactions of corresponding simplicity. The histologic nature of any neuron is determined, not by the general function of the system to which it belongs, but solely by the specific manner in which it itself is employed. Histologic differences in neuron types are quantitative rather than qualitative. In cell bodies and dendrites histologic differences correspond to quantitative differences in environment, differences in the number of sources of stimulation, in the extent to which these are used and in the extent to which these sources are differentiated into distinct fields of reception.

ANGINA PECTORIS

RELIEF OF PAIN BY PARAVERTEBRAL ALCOHOL BLOCK OF THE UPPER DORSAL SYMPATHETIC RAMI *

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BOSTON

ANATOMY AND PHYSIOLOGY OF CARDIAC NERVES

Following the work of Langley,[1] it is generally believed that the sympathetic sensory and motor nerve supply to the heart and ascending aorta is derived from the upper dorsal segments of the spinal cord. Both afferent and efferent fibers cross from the cord to the prevertebral sympathetic ganglia by the white rami communicantes (fig. 1). The cervical nerves possess gray rami only, and therefore are not concerned with cardiac pain, while from the sixth dorsal down the sympathetic fibers enter the splanchic nerves to the abdominal viscera. There is still no unanimity of opinion, however, as to how the cardiac motor and sensory fibers get from the upper dorsal sympathetic trunk to the heart and therefore how best to interrupt them surgically.

Following the ideas of François Frank, most surgeons have operated on the cervical sympathetic trunk. Jonesco thought that its complete removal from the stellate to the superior cervical ganglion was harmless and would cause a complete sensorimotor denervation of the heart. Danielopolu,[2] however, stated that it is unsafe to cut the cardiac accelerator fibers, all of which he assumed pass through the stellate ganglion and inferior cardiac nerves. Following his suggestions, Leriche,[3] Hofer,[4] and most other European surgeons have limited their operations to cutting the upper rami of the stellate ganglion to the brachial plexus, the vertebral nerve and more or less of the upper cervical sympathetic trunk with its branches which descend into the thorax or anastomose

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1. Langley, J. N.: The Sensory Nerve Fibers of the Heart and Aorta, Lancet **2**:955, 1924.

2. Danielopolu, D.: L'angine de poitrine et l'angine abdominale, Paris, Masson & Cie, 1927.

3. Leriche, R.: La chirurgie de la douleur et ses résultats, Presse méd. **35**: 497 and 561 (April-May) 1927.

4. Hofer, G.: Zur Chirurgie der Angina pectoris, Wien. med. Wchnschr. **78**:313 and 354 (March) 1928.

with the vagus. In this country, Coffey and Brown [5] have thought that by removing only the superior cervical ganglion they were able to relieve anginal attacks with a minimum of surgical intervention. Holmes and Ranson [6] expressed the belief that this interrupts vasoconstrictor fibers running in the superior cardiac nerve to the coronary arteries. Subsequent results have proved that this limited procedure is not nearly as effective as the more extensive removals of the lower cervical sympathetic employed in Europe. But no matter which of these operations is used, owing to the numerous anastomoses of the cardiac nerves in the neck with each other, with the inferior laryngeal nerve and the vagus, and the frequent anatomic variations, it is almost impossible to interrupt

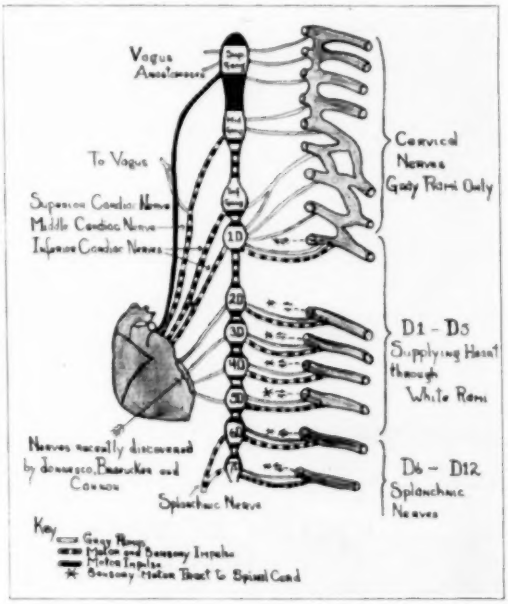

Fig. 1.—Diagram to show the connection between the central nervous system with the cervicodorsal sympathetic trunk and the nerves running from the trunk to the heart. The nerves described by Braeucker, Jonesco, Enachesco and Cannon, connecting the upper dorsal ganglia directly with the heart, are sketched in outline as it is not yet definitely known whether they are sensory as well as motor. The motor nerves are represented by the black solid lines; the combined motor-sensory nerves by the black and white lines, and the gray rami by the white lines.

all of these tracts by any operation limited to the neck. I believe that this accounts for the lack of uniform results in the literature on surgical intervention in angina pectoris.

5. Coffey, W. B., and Brown, P. K.: The Surgical Treatment of Angina Pectoris, Arch. Int. Med. **31**:200 (Feb.) 1923.

6. Holmes, W. H., and Ranson, S. W.: Surgical Sympathectomy in Angina Pectoris, J. Lab. & Clin. Med. **10**:183, 1924.

Recent anatomicophysiologic research has shown that all of these operations have further defects. Braeucker,[7] in Hamburg, and D. Jonesco and Enachesco,[8] in Bucharest, have demonstrated direct postganglionic connections between the upper thoracic sympathetic trunk and the heart. This has been corroborated from the physiologic point of view by Cannon, Lewis and Britton,[9] who have shown that the heart rate can still be accelerated after excision of both stellate ganglia, even when connections with both vagi and both adrenals have been removed. Cardiac acceleration in the cat is completely lost only when the rami of the upper nine dorsal nerves have all been cut.

On the purely sensory side, Spiegel,[10] in Vienna, has shown that removal of the upper cervical sympathetic in a dog has no effect in blocking pain which he produced by stretching the ascending aorta. This can be relieved only by removal of the stellate ganglia or by dividing the rami of the upper five dorsal nerves.[11]

With these points in mind, what is the best way to block the pain of angina pectoris? It is known that the left-sided pain is referred from the heart to the upper five or six segments of the dorsal cord, that its chief conduction path is via the inferior cardiac nerves and stellate ganglion to the upper thoracic chain, that a part probably descends the lower cervical sympathetic trunk from the middle cardiac nerve, and that a third portion may cross directly from the heart to the upper dorsal ganglia. From these ganglia the pain fibers enter the spinal cord by the white rami communicantes.

As pointed out by Mackenzie,[12] Langley [1] and Swetlow,[13] no operation limited to the cervical sympathetic can cut all these pathways.

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7. Braeucker, W.: Der Brustteil des vegetativen Nervensystems und seine klinische chirurgische Bedeutung, Beitr. z. Klin. d. Tuberk. **66**:1 (March) 1927.

8. Jonesco, D., and Enachesco, M.: Compt. rend. Soc. de biol. **97**:977 and 980, 1927.

9. Cannon, W. B.; Lewis, J. T., and Britton, B. W.: A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion with Evidence for Accessory Accelerator Fibers from the Thoracic Sympathetic Chain, Am. J. Physiol. **77**:326, 1927.

10. Spiegel, E. A.: Experimentelle Neurologie, Berlin, S. Karger, 1928.

11. I have purposely not discussed the rôle of the vagus nerve in angina pectoris. There is fairly good evidence that it is not implicated in the attacks as its motor function is purely depressor, and there are several reports of its having been cut or blocked on the left side during the course of an attack without any relief of pain. Hofer (Wien. med. Wchnschr. **78**:313 and 354, 1928), who has frequently cut the depressor branch of the vagus, has given up this limited procedure.

12. MacKenzie, J.: A Critique of the Surgical Treatment of Angina Pectoris, Lancet **2**:695, 1925.

13. Swetlow, G. I.: Paravertebral Block in Cardiac Pain, Am. Heart J. **1**:1 (April) 1926.

CLINICAL STUDIES

It can be shown from the foregoing summary of the present knowledge of cardiac enervation that there are three surgical procedures which are theoretically capable of blocking all the cardiac pain tracts to the spinal cord: (1) removal of the stellate with the upper thoracic sympathetic ganglia; (2) cutting or blocking the corresponding rami communicantes, and (3) cutting the corresponding posterior spinal nerve roots.

The third is the only method which preserves the cardiac accelerator tracts, and my colleagues and I are planning to try it whenever we have a patient who presents a reasonable surgical risk. Excision of the prevertebral sympathetic ganglia has become a surgical possibility by the approach described by Adson and Brown for excision of the stellate and second dorsal ganglia in Raynaud's disease.[14] We have recently used it in a case of severe angina pectoris in a man, aged 20, with aortic regurgitation but with good heart muscle. He has been completely relieved of painful attacks to date (one month), but the operation is much too severe a surgical procedure to employ in the usual case of angina pectoris.

The second method mentioned is by far the easiest to carry out; it can be done either by direct cutting of the white rami or by paravertebral injection. Injection was first performed by Mandl[15] in Vienna, in 1924, with procaine hydrochloride. All the injections gave relief, but the duration of the relief varied from only a few hours to eleven months. This method is still in use in Vienna. We have tried procaine alone four times, and on each occasion we obtained relief which lasted thirty-six hours. The attacks then resumed their previous course.

Swetlow[13] employed the same method but used alcohol. His reported seventeen cases have shown results as good or better than those obtained by radical operations—they will be summarized with my own. Eleven injections were given at the cardiac clinic of the Massachusetts General Hospital; the first five were given by me[16] in 1927, the others by Dr. Mixter in 1928.

TECHNIC OF PARAVERTEBRAL INJECTIONS

The technic of the paravertebral injection that I have used is that described by Labat in his textbook.[17] For typical left-sided angina it

14. Brown, G. E., and Adson, A. W.: Physiologic Effects of Thoracic and Lumbar Sympathetic Ganglionectomy or Section of the Trunk, this issue, p. 322.

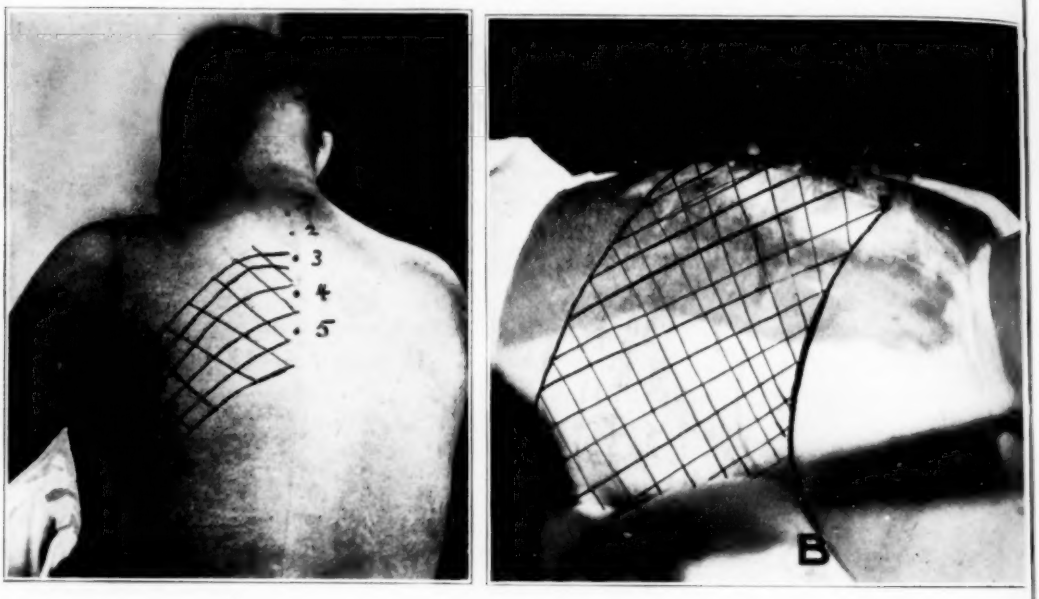
15. Mandl, F.: Die Wirkung der paravertebralen Injektion bei Angina pectoris, Arch. f. klin. Chir. **136**:495, 1925.

16. White, J. C., and White, P. D.: Angina Pectoris: Treatment with Paravertebral Alcohol Injections, J. A. M. A. **90**:1099 (April 7) 1928.

17. Labat, G.: Regional Anaesthesia, Philadelphia, W. B. Saunders Company, 1924.

is performed on the upper five left dorsal nerves just lateral to the intervertebral foramina.

Briefly, it consists in having the patient lie on the right side, with his legs drawn up as for lumbar puncture. The back is painted with iodine and the spines of the upper five dorsal vertebrae are palpated and marked with acriflavine (acriflavine on iodine gives a jet black sterile mark) (fig. 2). Next, corresponding dots are made 4 cm. to the left of each dorsal spine. An intradermal injection of procaine is made at each of these points. Through each wheal a thin needle of 8 or 10 cm, not attached to a syringe, is advanced perpendicularly to the plane of the skin. It should touch the upper border of the underlying rib. A few drops of procaine are injected to desensitize the periosteum and the tip of the needle is shifted until it slips by the lower border of the rib. It is then changed so that



A B

Fig. 2.—*A*, back of the patient in case 1 to show the points of injection 4 cm. to the left of the spinous processes, and the characteristic anesthesia. The descending cervical nerves overlap and obscure the anesthesia of the upper two or three segments. This man showed a typical Claude-Bernard-Horner syndrome as well. *B*, the back of the same patient in final right-sided injection when D_3 to D_7 were injected. The cross-hatched lines mark the posterior area of skin anesthesia. The five needles are in position.

it points medially and toward the feet at an angle of 45 degrees (fig. 3). Then it is pushed in exactly 2 cm. farther. It should now lie in the center of the intercostal space near the artery, vein and nerve, close to the point of origin of the sympathetic rami. Aspiration suffices to prove that the needle has not punctured a blood vessel or any abnormal prolongation of the subarachnoid space, while injection of a few drops of procaine produces a cough reflex if the pleura has been punctured. In either event, no harm is done if the condition is recog-

nized and the needle shifted. I have used five needles and injected 5 cc. of 1 per cent procaine into each,[18] leaving all five in position. This should give a characteristic anesthesia of the wall of the chest and the axilla within ten minutes. If this does not appear, the position of the needles must be corrected; whereas if anesthesia is complete, 5 cc. of 80 per cent alcohol is injected into each intercostal space and the needles are withdrawn.

It should be emphasized that this is a fairly difficult and potentially dangerous procedure. The injection must be made within a few millimeters of the parietal pleura and close to the intervertebral foramen. It is therefore important to learn the technic thoroughly by preliminary

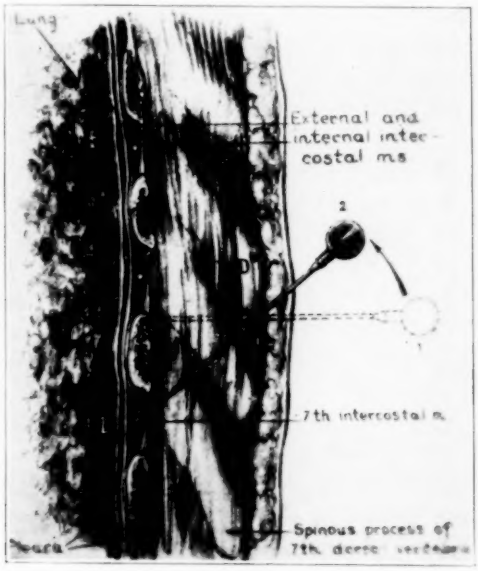


Fig. 3.—1, first position of the needle taking contact with the rib; 2, second position after advancing the needle beyond the lower border of the rib (from Labat's textbook on Regional Anesthesia, Philadelphia, W. B. Saunders Company, 1924, p. 229.

injections of methylene blue (methylthionine chloride, U. S. P.) into the cadaver, and to exercise extreme care in its clinical application.

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18. Five cubic centimeters of alcohol causes an area of necrosis about 1 cm. in diameter, whereas 5 cc. of novocaine diffuses over a much wider area, and may cause anesthesia beyond the zone to which the alcohol can penetrate. Some of my failures to secure a complete block with alcohol after a successful injection of procaine are probably due to this. Hereafter, I intend to inject only 2 cc. of 2 per cent novocaine, which will require a much closer contact with the intercostal nerve.

SUMMARY OF CASES

Table 1 summarizes the clinical results of the paravertebral injections of alcohol. All of the patients were selected by Dr. Paul D. White as being the most severe and obstinate cases of angina pectoris at the cardiac clinic. No patient was refused on account of being too sick, although many had angina while at complete rest in bed, and had had previous attacks of coronary thrombosis.

Few comments are necessary. The poor results of injection into the right side in case 1 and into the left side in case 3 can be accounted for by failure to secure a lasting anesthesia with the alcohol—sensation over the peripheral distribution of the spinal nerves affected by the injection returned after the effects of the procaine had worn off. Case 3 is that of a Jewish woman, who is so nervous that no one has been able to make out how much of the pain of which she now complains is anginal. The second patient was pleased with the result for six months; there was then a recurrence of anginal attacks with increasing severity until death during an attack nine months after the injection. In cases 9 and 10 the injections were made during the course of severe anginal attacks, and it was interesting to note that in each the symptoms ceased abruptly as the injection was made into the third dorsal nerve.

I had not expected complete relief to last for more than six months, but the first patient has not had an attack of left-sided pain for twenty-two months; the Claude-Bernard-Horner syndrome in this case lasted a year. A contracted pupil and narrowed palpebral fissure following injection is a good sign, and has been present in two of three of the patients who have shown 100 per cent of relief. The skin anesthesia of the wall of the chest, on the other hand, usually lasts only a few weeks, and is then replaced by hyperesthesia which lasts for nearly a month. This is always more or less troublesome; in one instance, the patient complained that it was as bad as the angina for a week.

Two patients had pleuritic pain for twenty-four hours after receiving the injection, and one had an alarming left-sided pallor of the face and low blood pressure for an hour, but there have been no more serious accidents to date. The fact that four patients have since died is not surprising considering the severity of the condition of the patients treated.

COMMENT

Any one who employs surgical treatment for angina pectoris is obviously playing with fire; one of Swetlow's prospective patients died the night before he had planned to make an injection. Danielopolu,[2] Hesse [19] and Leriche [3] claimed that blocking the accelerator nerves can be done safely in normal people, but that it is dangerous in patients

19. Hesse, E.: Beitr. z. klin. Chir. **141**:321, 1927.

TABLE 1.—*Patients Treated by the Paravertebral Injection of Alcohol at the Massachusetts General Hospital.*

Case	Age	Diagnosis	Treatment	Results	Degree Relieved, per Cent	Duration	Status at Last Report
1	54	Syphilitic aortitis, aortic regurgitation, hypertension, angina pectoris; confined to bed	Left 2/19/27; right 3/20/28	Left-sided relief; development of right-sided pain, no relief	100 (left side) 0* (right side)	To date	Up and about but unable to work; moderate attacks of right-sided pain
			12/20/28	.....	75 (right side)	To date	Rare mild attack right-sided pain; no left-sided pain
2	60	Hypertensive and arteriosclerotic heart disease, aortic regurgitation, angina pectoris, previous attack of coronary occlusion, slight congestive failure	Left 5/16/27; reinjection 6/23/27	Considerably relieved; further relief	50	To death	Able to resume light work until sudden death, undoubtedly from coronary thrombosis or angina pectoris on Feb. 8, 1928; no autopsy
3	53	Arteriosclerotic heart disease, hypertension, angina pectoris at rest	Left 6/9/27	Relief slight but definite; difficult to judge because of extreme nervousness	20 *	To date	Up and about, quietly active, appearing in good health but with moderate angina pectoris (November, 1928)
4	54	Moderate arteriosclerosis and enlarged heart; angina pectoris; incapacitated	Left 7/22/27	Left-sided relief; mild right-sided attacks	100	To date	In fair health, but still has right-sided angina pectoris; has resumed work as truck driver
5	59	Arteriosclerotic heart disease, hypertension, myocardial insufficiency, previous coronary thrombosis	Left 8/12/27	Relief partial	25	To death	Died suddenly on Jan. 9, 1928, undoubtedly of coronary thrombosis or angina pectoris; no autopsy
6	52	Hypertensive heart disease, aortic regurgitation, angina pectoris at rest	Left 11/5/27	Complete relief at first; later slight recurrence	100 90	To date	Comfortable and able to do light work (Aug. 1, 1928)
7	58	Arteriosclerotic heart disease, hypertension, angina pectoris	Right 3/3/28	Considerable relief	65	To date	Fairly comfortable and has resumed light work (August, 1928)
8	68	Arteriosclerotic heart disease, hypertension, angina pectoris, previous coronary thrombosis	Left 4/17/28	Partial relief at first, then recurrence; judgment of case somewhat difficult because nervousness	75 50	To date	Uncomfortable, angina pectoris daily but able to be quietly up and about (July, 1928)
9	47	Hypertension, arteriosclerosis, coronary thrombosis, angina pectoris; confined to bed	Left 9/4/28	Complete relief of attacks	100	To death	Died of myocardial failure with angina on Nov. 4, 1928
10	51	Arteriosclerotic heart disease, coronary thrombosis, angina pectoris, morphinism	Left 9/14/28	Relief of attacks	...	To death	Five days later another attack of coronary thrombosis; died October 4; died too soon to include in series

* Inadequate anesthesia from alcohol. Poor result probably due to failure in technic.

with angina pectoris. They pointed to the 19 per cent of early mortality in the Jonesco operation from acute decompensation and pulmonary edema. On the other hand, Cutler [20] and Cannon and Britton [21] have shown that dogs and cats can stand removal of both stellate ganglia, and (in Cannon's cats) the entire sympathetic chain on both sides as well, and still respond to exercise by a rise in pulse rate from the effect of epinephrine and checking of the vagus inhibitive impulses. This is certainly an important question and requires careful study. In my cases I have seen no tendency to early cardiac decompensation, and the patient in case 1 has shown a normal increase in pulse rate with exercise and no evidence of further myocardial injury by an electrogram taken twenty months after injection.

Another objection to the injection of alcohol paravertebrally is the proximity of the pleura and spinal cord, but results to date show that this danger is slight when one is experienced in the technic. The hyperesthesia of the wall of the chest mentioned seems to be unavoidable, and is always troublesome for several weeks.

In favor of the method are: its simplicity in comparison to a radical operation, the slight degree of disability to the patient, who can resume his normal activity within a day or two, and the fact that it can be used with more comparative safety on patients with severe cases of angina than could any form of operation. Some have objected that the effect of alcohol would be short-lived, but I have two patients who have been completely relieved from pain for twenty-four and twenty months, respectively, which is ample time for the nerves to regenerate if they are ever going to do so. As the rami communicants are thin, finely myelinated structures, I believe that with effective injections the sympathetic paths can be destroyed permanently. Furthermore, if pain should recur there is no contraindication to repetition of the injection; several of my patients have already requested this if they should have a severe recurrence.

To show the relative merits of paravertebral alcohol block and operation, table *2* compares the statistics in cases in which injections were made by Swetlow, Mixter and White with the operative statistics assembled by Richardson,[22] Cutler [20] and Fontaine.[23]

There is no question but that after operation the disability and the immediate postoperative mortality are greater. Cutler had limited his

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20. Cutler, E.: Summary of Experience Up to Date in the Surgical Treatment of Angina Pectoris, Am. J. M. Sc. **173**:613 (May) 1927.

21. Cannon, W. B., and Britton, W. S.: Influence of Motion and Emotion on the Medulli-Adrenal Secretions, Am. J. Physiol. **79**:433, 1927.

22. Richardson, E. P., and White, P. D.: Sympathectomy in the Treatment of Angina Pectoris, Am. J. M. Sc., to be published.

23. Fontaine, R.: Les résultats actuels du traitement chirurgical de l'angine de poitrine, Thèse de Strasbourg, 1925.

percentage of operative deaths to cases with death in the first twenty-four hours, but I have thought that four days is a fairer period to allow for the disintegration of a damaged heart. This has increased his figures for deaths after complete sympathectomy so that they agree with those published by Fontaine in his thesis (table 2.) It shows, as Danielopolu and Leriche have pointed out, that this radical operation is extremely dangerous. I believe that this is not necessarily because of interruption of the cardiac accelerator nerves alone, but also because patients with severe angina pectoris would be poor risks for any type of operation of corresponding severity and duration.

TABLE 2.—*Relative Merits of Paravertebral Alcohol Block and Operation*

Paravertebral Injections of Alcohol					
			Massachusetts General Hospital		Swetlow
Number of injections			11		17
Relief	100 to 90%	Good	36.4	72.8%	53
	90 to 50%		36.4		35
	50 to 25%	Improved	9.1%		—
	25 to 0	Failures	18.1%		12%
Deaths			0		0
Average number of days in hospital			3 to 5		3 to 5

Operations for Angina Pectoris						
	Total Sympathectomies			Partial Sympathectomies		
	Massachusetts General Hospital	Cutler	Fontaine	Massachusetts General Hospital	Cutler	Fontaine
No. of operations	2	27	37	8	53	57
Results: Good	50%	63%	57%	37.5%	41.5%	67%
Results: Improved	—	18.5%	11%	—	35.8%	12.3%
Results: Failures	—	7.4%	8%	50%	11.2%	11%
Deaths	50%	22%	19%	12.5%	7.5%	7.5%
Days in hospital	7 to 12	—	—	7 to 12	—	—

CONCLUSION

Much work remains to be done in the treatment for angina pectoris by paravertebral alcohol block, both in perfection of technic, to enable accurate injections into the rami and in making sure that the heart is not injured by the blocking of its accelerator nerves. Much also remains to be investigated in the field of the anatomic physiology of heart enervation. For instance, one does not know definitely whether the relief from attacks of angina results from blocking of the motor impulses or from interruption of the sensory afferent tracts. As the two pathways are separated only at their point of entrance to the spinal cord, I hope to get some information by cutting the sensory tracts alone in the posterior roots, provided I can find a patient with severe angina pectoris

who is a good enough surgical risk to justify laminectomy. Also one does not know the mechanism of anginal pains referred to the neck and jaw, and whether dorsal block alone is capable of giving relief. Penfield [24] reported the case of a patient who was completely freed from attacks in the chest and arm by removal of the lower cervical sympathetic, but pain referred to the neck and jaw remained unchanged. Presumably, the injection of alcohol into the upper dorsal rami would not have relieved the condition, but would likewise have had to be supplemented by resection of the superior cervical ganglion.

As in a successful sympathectomy, the best one can do for the patient is to rid him of pain; one cannot thereby restore the diseased heart to normal. Granted these limitations, the more I have seen of injections of alcohol, the more confident I have become that this is a logical and safe method of treatment in severe forms of angina pectoris. The method in its present status gives promise of being distinctly less dangerous and of giving results as good, if not better, than sympathectomy.

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24. Penfield, W.: The Neurological Mechanism of Angina Pectoris and Its Relation to Surgical Therapy, Am. J. M. Sc. **170**:864, 1925.

THE RÔLE OF THE SYMPATHETIC NERVOUS SYSTEM IN PAINFUL DISEASES OF THE FACE*

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Interest in the possible rôle of the sympathetic nervous system in the production or transmission of painful sensations in the face was aroused by the failure of therapeutic measures, directed against the trigeminal nerve, to afford relief in cases of so-called atypical neuralgia. This group is ill defined and undoubtedly includes painful conditions of diverse origin. It is also probable that the different sensations of pain are transmitted over different nerves. In this paper I have attempted to indicate one type, those possibly of trigeminal tract origin, which may be separated from the group of atypical neuralgias.

The symptomatology of the so-called atypical neuralgias is characterized by its diversity, probably because no one has been able to distinguish the various types. Certain characteristics, however, are common to the majority of cases. The pain is generally described as a dull, aching, burning or pressure pain with exacerbations of greater intensity. Glaser [1] compiled sixty-four descriptive adjectives used by 143 patients. In contradistinction to major trigeminal neuralgia, the pain in the atypical cases is seldom referred to the anatomic limits of any branch of the fifth nerve. In fact, if one eliminates a few cases which I am inclined to believe are of fifth nerve origin, although not related to trigeminal neuralgia, none of the so-called atypical neuralgic pains follows any known anatomic distribution. The temple, the cheek and the deep parts within the orbit are the regions usually affected. The lower jaw may be involved, but less often than the upper. The pain frequently spreads to the posterior auricular and mastoid regions, and in some patients to the neck and arm. It is always felt in the deeper tissues, never on the surface as in trigeminal neuralgia.

The pain is usually continuous for several hours, appearing in some cases at irregular intervals, in others with great regularity. In exceptional cases the pain may persist without intermission for months or

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1. Glaser, M. A.: Atypical Neuralgia, So Called: A Critical Analysis of One Hundred and Forty-Three Cases, Arch. Neurol. & Psychiat. **20**:537 (Sept.) 1928.

years. It varies considerably in severity, and exacerbations of great intensity, especially when the patient is tired, nervous or excited, are the rule. No trigger zones exist, and no form of external stimulation has a bearing on the pain. Headaches, sometimes of the migrainous or hemicranial types, are rather frequently associated with the atypical neuralgias, but the two may not appear coincidentally and many patients are never so affected. Flushing of the face, lacrimation and other phenomena suggestive of sympathetic origin are frequently noted.

Are these atypical neuralgias of organic or functional nature? The neurologist and psychiatrist generally consider them the latter, but the usual lines of treatment based on this conception have signally failed. A few probably belong in the group of neuroses, but some painful diseases, long considered as belonging to this group, may, in the light of recent work, be classified as of sympathetic origin. I refer particularly to the suggestive results obtained by von Gaza, and repeated by Scrimger and Archibald,[2] in cases of vague abdominal pains. These authors reported relief of such pains by section of certain thoracic white rami. If this work is substantiated it indicates that these pains are either of sympathetic origin or are transmitted over sensory fibers which are incorporated in the sympathetic white rami.

If one is unwilling to consider all cases of atypical neuralgia as psychogenic in origin, the pain is either of central type or due to some peripheral lesion. If the latter, the existence of some tangible course for the transmission of the painful sensation must be admitted. In the face one is limited anatomically to three possibilities—the trigeminal, the facial and the sensory fibers accompanying the sympathetic nerves. The location of the lesion is equally uncertain. If peripheral, however, one is practically limited to a lesion in the gasserian, geniculate or sympathetic ganglia, or to a disease of their branches. In addition, it is possible that the ganglion nodosum of the vagus sends some fibers to accompany the sympathetic.

The fifth nerve naturally attracted first attention, but with a clearer conception of the symptomatology of trigeminal neuralgia the radical differences in the type of pain in typical and atypical neuralgias was recognized. In spite of these differences, several surgeons have sectioned the sensory root of the gasserian ganglion in cases of atypical neuralgia, but with almost uniform failure to afford relief. The fact that in all known diseases of the gasserian ganglion or its branches the pain is referred to the extreme distal distribution of the particular nerves

2. Archibald, Edward: Effect of Sympathectomy upon the Pain of Organic Disease of Arteries of the Lower Limbs and for Obscure Abdominal Pain, Ann. Surg. **88**:499 (Sept.) 1928.

involved, while in the usual atypical neuralgias such an anatomic limitation does not exist, proves conclusively that the fifth nerve plays no rôle in these atypical diseases.

Occasionally a diagnosis of atypical neuralgia is made in which the pain actually follows completely the distribution of one or more branches of the gasserian ganglion. It is this group that I consider as of possible central trigeminal origin. The pain is deepseated, continuous and frequently described as a pressure pain, thus resembling the usual atypical case. I believe that it is of trigeminal origin because of its exact anatomic distribution. Relief has been afforded in some cases by the deep injection of alcohol. The following case history illustrates this type of neuralgia. The patient was first examined eighteen months ago.

REPORT OF CASES

Case 1.—For seven years, this patient, a woman, had had constant burning, pressing pains in the entire distribution of the maxillary branch on the left, and for six and one-half years a similar pain on the right. There were frequent exacerbations, characterized by great intensity of pain and flushing of the face, but at no time had the pain entirely ceased. Bilateral injections of alcohol were made at the foramen rotundum. Immediate anesthesia and complete relief of pain was obtained on the right, the relief continuing to date. Incomplete anesthesia, but temporary relief of pain, was obtained on the left. In a few days pain returned on this side. Intracranial section of the second division is now recommended.

Even though the atypical pain is confined to the distribution of the fifth nerve, relief may not be obtained by section of the sensory root of the gasserian ganglion.

Case 2.—I performed this operation in March, 1923, on a patient who complained of an intense, burning pain, of one year's duration, in the entire distribution of the second and third divisions of the left gasserian ganglion. The pain was constantly present, with exacerbations, especially when the patient was tired. The atypical nature of the pain was recognized and the operation performed reluctantly. For a few weeks he was free from pain; then it returned in its original intensity. In February, 1925, the superior cervical sympathetic ganglion was excised and the adventitia stripped from the common, internal and external carotid arteries without benefit. The pain is unchanged today, although he has tried numerous drugs and suggestive treatment.

The persistence of pain in this and similar cases after section of the sensory root of the gasserian ganglion does not prove that it is not of trigeminal origin, but simply that these sensations are not transmitted through the ganglion and the sensory root. A similar persistence of pain sometimes follows section of the sensory root in cases of postherpetic trigeminal neuralgia.[3] In fact, pain in the latter disease may

3. Peet, M. M.: Postherpetic Trigeminal Neuralgia: Persistence of Pain after Section of the Sensory Root of the Gasserian Ganglion, J. A. M. A. **92**:1503 (May 4) 1929.

closely resemble the particular type of atypical neuralgia under consideration. The persistence of postherpetic pain after section of the sensory root proves that pain of central origin can be referred to the periphery of the trigeminal division, even though the pathway for its transmission has been interrupted. On analogous grounds, it appears probable that this particular type of atypical neuralgia is of trigeminal origin, the lesion being in the trigeminal tract in the medulla or the pons.

According to Sluder,[4] many atypical pains in the cheek, upper jaw, lower jaw and retro-auricular regions are due to irritation of the sphenopalatine ganglion. Further work, however, has tended to disprove his assertions. Both Cushing [5] and Frazier [6] showed that excision of Meckel's ganglion, a more certain method than the injection of alcohol, fails to relieve in these cases. I do not deny the existence of the Sluder syndrome, although I do not believe it to be of sphenopalatine ganglion origin. It should be considered as one type of atypical neuralgia, the origin of which is unknown.

The possible rôle of the facial nerve in atypical neuralgias is still uncertain. Hunt [7] showed that sensory fibers from the geniculate ganglion supply certain portions of the ear, and Ruskin [8] claimed an intra-oral distribution. I have frequently stimulated the great superficial petrosal nerve, both by direct pressure before and after its division and by a weak electrical current. When the stimulus is applied to the proximal end the patient has invariably complained of severe pain deep within the ear, and on one occasion pain was also referred to the back of the mouth. This induced pain, however, does not resemble the type associated with the atypical neuralgia. This, in a way, eliminates from consideration the great superficial petrosal nerve and its component in the sphenopalatine ganglion. The facial nerve also carries deep pressure

4. Sluder, G.: Headaches and Eye Disorders of Nasal Origin, St. Louis, C. V. Mosby Company, 1918.

5. Cushing, Harvey: The Major Trigeminal Neuralgias and Their Surgical Treatment Based on Experiences with 332 Gasserian Operations: The Varieties of Facial Neuralgia, Am. J. M. Sc. **160**:157 (Aug.) 1920.

6. Frazier, C. H., and Russell, E. C.: Neuralgia of the Face: An Analysis of Seven Hundred and Fifty-Four Cases with Relation to Pain and Other Sensory Phenomena Before and after Operation, Arch. Neurol. & Psychiat. **11**:557 (May) 1924.

7. Hunt, J. R.: The Sensory System of the Facial Nerve and its Symptomatology, J. Nerv. & Ment. Dis. **36**:321 (June) 1909; The Sensory Field of the Facial Nerve: A Further Contribution to the Symptomatology of the Geniculate Ganglion, Brain **38**:418 (Dec.) 1915.

8. Ruskin, S. L.: The Sensory Field of the Facial Nerve, Arch. Otolaryng. **7**:351 (April) 1928; The Sensory Field of the Facial Nerve: Intra-Oral Representation, Bull. New York Acad. Med. **3**:409 (June) 1927.

sensation from the entire face.[9] Since the discomfort in atypical neuralgia is commonly described as a pressure pain, the possibility that this sensation is transmitted over the facial nerve must be seriously considered. Proof will await the observation of a patient suffering with atypical neuralgia who subsequently develops a complete facial paralysis. Experimental temporary paralysis by the injection of procaine hydrochloride probably is of little value, since the injection must be extracranial. It is possible that pressure pain sensations may be transmitted along the fibers carrying muscle sense, which pass centrally along the motor root. At present, evidence that a lesion in a facial nerve can produce the pain of atypical neuralgia, or that the painful sensation may be transmitted over this nerve, is entirely lacking.

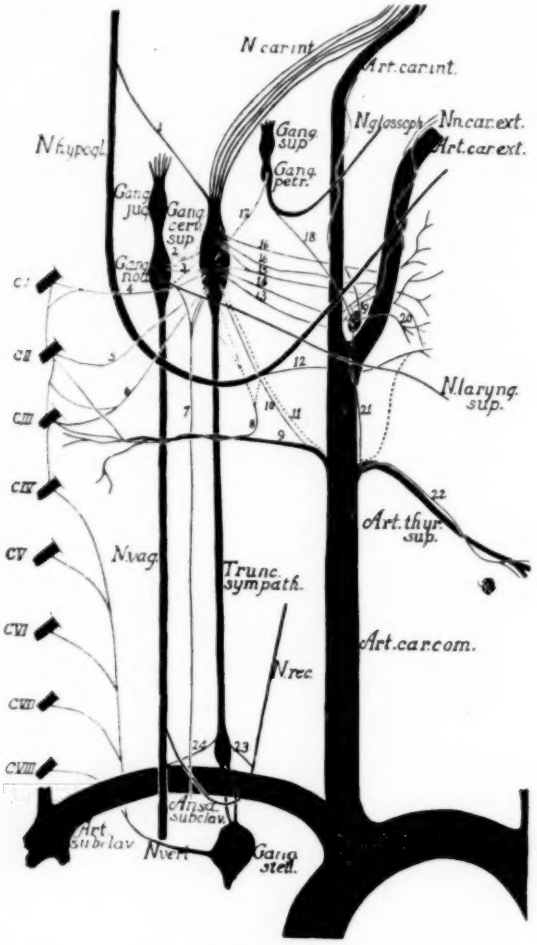
By the process of exclusion, there remains only the sympathetic nervous system as a possible source of painful diseases of the face. According to the present conception, the function of the sympathetic nervous system is entirely the transmission of efferent nerve impulses. If this view is accepted, the sympathetic system may produce pain by vasomotor spasm, but the recognition of such painful sensations must be transmitted to the brain over other nerves. These must be at least grossly associated with the sympathetic fibers; otherwise, one has to assume that the afferent impulse passes over the trigeminal or facial nerves.

It is well known that sensory fibers from the spinal nerves accompany, and in many instances are incorporated in, the sympathetic nerves in other parts of the body. In fact, some sympathetic nerves, like the great splanchnic nerve, contain a large number of fibers from the thoracic posterior root ganglia. No fibers positively identified as sensory have been found passing to the superior cervical sympathetic ganglion, but there are numerous branches from this ganglion which pass to the glossopharyngeal, vagus and hypoglossal nerves, and to certain sensory branches from the vagus and upper cervical nerves. It is possible that these sensory fibers accompany the sympathetic nerves in the head as they do in other regions.

The group of nerve fibers (labeled 2 in the accompanying figure) passing between the ganglion nodosum of the vagus and the superior cervical sympathetic ganglion are of special interest. Whether these fibers are of sympathetic or vagus origin has not been determined. Degeneration experiments will be made to determine this point. At present one can only theorize regarding these fibers, but certain data already accumulated suggest their sensory nature. In one patient suffer-

9. Ivy, R. H., and Johnson, L. W.: Preservation of Deep Sensibility of the Face after Destruction of the Fifth Nerve, Univ. Penn. M. Bull. **20**:35 (May) 1907. Davis, L. E.: The Deep Sensibility of the Face, Arch. Neurol. & Psychiat. **9**:283 (March) 1923.

ing from severe, constant pain in the cheek, just below the zygoma, electrical stimulation and pinching of these fibers aggravated the pain. It immediately stopped when the fibers were cut. This patient had had atypical neuralgia intermittently for several years, but for the past six



Diagrammatic representation of the cervical sympathetic trunk and of the branches of the superior cervical sympathetic ganglion in the cat: *1*, branch to the hypoglossal nerve; *2*, fibers connecting the superior sympathetic ganglion and the ganglion nodosum of the vagus; *3*, fiber from the vagus to a branch of the sympathetic system; *4*, *5* and *6*, gray rami to the cervical nerves; *7*, gray ramus to a branch of the common carotid artery (from Billingsley and Ranson).

months it had been constantly present, although varying much in intensity. Although it was comparatively mild at the time of operation, stimulation of the fibers between the vagus and sympathetic ganglia

increased its intensity to the maximum suffered previously. This induced pain was in the location and of the same quality as the atypical neuralgia. Whether this pain should be considered of sympathetic or of vagus origin is not certain since one does not know the course of the fibers stimulated. If they are of vagus origin they must ascend with branches from the superior sympathetic ganglion, since Ranson and Billingsley [10] showed that there are no descending fibers in the cervical sympathetic trunk. These authors [11] also showed that there are no preganglionic fibers in the branches of the superior sympathetic ganglion. One must therefore assume that the fibers between the nodosum and sympathetic ganglia are either gray rami from the latter, or sensory fibers from the vagus which merely pass to the sympathetic ganglion on their course to the head. In other words, the connection is only a gross anatomic one.

I have thus far considered the sympathetic system in relation to atypical neuralgias only from its gross anatomic structure, ignoring the fact that the chance inclusion of sensory fibers from other nerves actually has no bearing on the function of the sympathetic nerves and therefore no relation to the possible sympathetic origin of atypical neuralgias.

From the modern neuro-anatomic standpoint, i.e., that the sympathetic nerves carry only efferent impulses, the sympathetic nervous system can play a rôle only in the atypical neuralgias of the face if such neuralgias are due to vasomoter spasm.

Sympathetic innervation of the external and internal carotid arteries, including the branches of the latter in the brain, has been definitely established. There is also considerable clinical material indicating the occurrence of spasms of these vessels. The missing link needed to complete the chain of evidence implicating the sympathetic in the atypical neuralgias is proof that such spasms cause such neuralgic pain. This proof is not entirely lacking. The well known pain due to vascular spasm in the extremities in many cases resembles the pain of atypical neuralgia in the face.

In some patients, Frazier [12] showed that electrical stimulation of the superior cervical sympathetic ganglion produces pain in the zone of the

10. Ranson, S. W.: An Introduction to a Series of Studies on the Sympathetic Nervous System, J. Comp. Neurol. **29**:305 (Aug. 15) 1918. Ranson, S. W., and Billingsley, P. R.: The Superior Cervical Ganglion and the Cervical Portion of the Sympathetic Trunk, ibid., p. 313.

11. Billingsley, P. R., and Ranson, S. W.: On the Number of Nerve Cells in the Ganglion Cervicale Superius and of Nerve Fibers in the Cephalic End of the Truncus Sympathicus in the Cat and on the Numerical Relations of Pre-Ganglionic and Post-Ganglionic Neurones, J. Comp. Neurol. **29**:359 (Aug. 15) 1918; Branches of the Ganglion Cervicale Superius, ibid., p. 367.

12. Frazier, C. H.: Pain Phenomena of the Face: Their Origin and Treatment, with Special Reference to Trigeminal Neuralgia, Long Island M. J. **21**:395 (July) 1927; Am. J. M. Sc. **169**:469 (April) 1925.

trigeminal distribution. I have confirmed this observation in a number of patients. The similarity between this induced pain and that of atypical neuralgia was demonstrated in the case previously referred to. This patient, in addition to the subzygomatic neuralgia, complained of a different type of pain in the region corresponding roughly to the temporal muscle. This pain fluctuated in intensity and had been present much of the time for several months. Section of the nerves between the nodosum and superior sympathetic ganglia stopped the pain in the cheek, but the temporal pain persisted. Under local anesthesia the superior cervical sympathetic ganglion was stimulated electrically and the pain in the temple was immediately aggravated. Similar stimulation of the internal carotid branches from the superior sympathetic ganglion increased the severity of the pain to a degree which he considered unbearable. This induced pain was exactly similar in location, type and intensity to the severe exacerbations of atypical neuralgia. The pain immediately ceased when the carotid sympathetic branches were divided.

The occurrence, as in this patient, of two distinct types of pain in two locations is not unusual. The interest lies in the accentuation of the pain—in the cheek by stimulation of the fibers between the nodosum and the superior cervical sympathetic ganglia, and in the temporal region by stimulation of the carotid plexus. This suggests that the difference in the pain in the two locations was due to a difference in etiology or transmission. Both types of pain were relieved by section of the nerves apparently involved.

Further suggestive evidence is furnished by the induction of, or an increase in the severity of, the neuralgic attacks when the patient is fatigued, and especially when worried, frightened or angered—emotions which are known to stimulate the sympathetic nervous system.

Fay called my attention to an interesting sign presented in some cases of atypical neuralgia. He found that irritation of the carotid and often of the temporal and occipital arteries by pressure produced pain in the regions supplied by them. The artery was often sensitive to pressure. Similar irritation on the opposite side produced no symptoms. The interpretation of this observation is not clear, but it suggests a vasomotor irritability, possibly on a sympathetic basis.

Section of the various branches of the superior cervical sympathetic ganglion has not been performed in a sufficient number of cases of atypical neuralgia to warrant drawing conclusions from the clinical data available. Frazier [13] reported ten cases, with favorable results in only one, and the ultimate outcome in this case is unknown. I believe that the majority of his cases should be classed as paresthesias, probably of

13. Frazier, C. H.: Atypical Neuralgia: Unsuccessful Attempts to Relieve Patients by Operations on the Cervical Sympathetic System, Arch. Neurol. & Psychiat. **19**:650 (April) 1928.

central trigeminal origin, and should not be included with the atypical neuralgias. Certainly, I should not have expected relief from section of the sympathetic nerves in most of those reported. My own experience is also too limited to permit definite conclusions. The evidence so far accumulated, however, suggests that the sympathetic nervous system, through vasomotor spasms, does play a rôle in the etiology of some cases of atypical neuralgia. The chief difficulty at present lies in an inability to differentiate the various diseases now grouped under this term. When such differentiation is possible, one will be able more intelligently to select the cases and decide on their suitability for operation on the sympathetic nerve. A sufficient number of cases representing a single type of atypical neuralgia will then be available and definite conclusions can be drawn.

SUMMARY

The term atypical neuralgia is unsatisfactory for two reasons: the pains are not neuralgic in character, and a number of unrelated conditions are probably grouped under the one designation.

Unless of central origin, pain referred to the face must involve the trigeminal, the facial or the sympathetic nerves.

The peripheral trigeminal tract has been eliminated from consideration by the persistence of atypical neuralgic pain after section of the sensory root of the gasserian ganglion.

One type of so-called atypical neuralgia should be considered of central origin, the lesion being probably located in the trigeminal tract in the medulla or the pons.

Sensory fibers from various nerves, especially the vagus, may be incorporated in certain sympathetic nerves, although proof of such association is lacking. If found they will furnish an explanation for the transmission of painful sensations from the blood vessels. Only in this gross anatomic sense can the sympathetic system be considered sensory.

Atypical neuralgic pain can be of sympathetic origin only if such pain is due to vasomotor spasm, since this system carries only efferent impulses. Certain observations, while not conclusive, suggest that some types of atypical neuralgia are of this origin. Somewhat similar pains, namely, those of vascular disease of the extremities, are certainly of sympathetic origin. The reception of the painful sensation, however, must be transmitted over sensory nerves.

PHYSIOLOGIC EFFECTS OF THORACIC AND OF LUMBAR SYMPATHETIC GANGLIONECTOMY OR SECTION OF THE TRUNK *

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The permanent vasomotor and other physiologic changes resulting from sympathetic lumbar ganglionectomy with ramisectomy or section of the trunk have stimulated investigation and clinical application. We first studied a group of patients with spastic paralysis and subsequently a group with vascular disturbances of the vasoconstrictor type, that is, Raynaud's disease, other vascular diseases such as thrombo-angiitis obliterans, scleroderma and, in one case, subacute polyarthritis. This report includes the preoperative and postoperative physiologic studies on a total of thirty-nine cases.

ANATOMY AND PHYSIOLOGY †

Ranson [1] summarized the anatomy of the sympathetic nervous system as follows:

> The sympathetic nervous system is an aggregation of ganglions, nerves, and plexuses through which the viscera, glands, heart, blood vessels and smooth muscle in other situations receive their innervation. The most conspicuous feature of the system is a pair of ganglionated nerve cords or sympathetic trunks, which extend vertically through the neck, thorax and abdomen. Each sympathetic trunk is composed of a series of ganglions bound together by short nerve strands. Every spinal nerve is connected with the sympathetic trunk of its own side by one or more gray rami communicantes through which it receives sympathetic fibers for the control of blood vessels, sweat glands and smooth muscles of the hair follicles situated within the territory of its distribution. The majority of the nerve fibers that take origin in the ganglions of the sympathetic chain are distributed through the gray rami and the spinal nerves.

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† This section appeared in practically the form here given in Adson and Brown: The Treatment of Raynaud's Disease, Surg. Gynec. Obst. **48**:583 (May) 1929, and is here reproduced for the sake of clearness.

1. Ranson, S. W.: Anatomy of the Sympathetic Nervous System with Reference to Sympathectomy, J. A. M. A. **86**:1886 (June 19) 1926.

The ganglia of the lower thoracic and abdominal portions of the chain are less concerned with visceral activity than with constriction of the peripheral blood vessels, erection of the hairs and secretory activity of the sweat glands. The upper thoracic and cervical ganglia, however, bear a more intimate relation to the thoracic viscera, since they contain the cells of origin of postganglionic fibers for these viscera.

Ranson continued:

The thoracic and upper lumbar nerves are connected with the sympathetic chain by white as well as gray rami communicantes. These white rami contain both afferent and efferent fibers. The latter take origin from cells in the gray matter of the spinal cord, travel through the ventral root and white rami, and enter the sympathetic system to terminate in synaptic relation with the nerve cells found in the sympathetic ganglion. They are often designated as preganglionic fibers, while those that arise in the ganglions and relay the impulses onward are called postganglionic. The gray rami contain postganglionic fibers; the white rami contain preganglionic fibers.

The majority of the preganglionic fibers turn either upward or downward in the sympathetic chain, and run for varying distances within it before ending in its ganglions. The cervical sympathetic trunk is composed exclusively of preganglionic efferent fibers, derived through the white rami from the upper thoracic nerves and ascending to terminate in the cervical sympathetic ganglions. The lumbar and sacral portions of the trunk are composed in the major part of descending fibers derived through the white rami from the lower thoracic and upper lumbar spinal nerves.

Those fibers of the white rami which are concerned with the innervation of the abdominal viscera pass into the splanchnic nerves and end in the celiac ganglion. These fibers reach the splanchnic nerves after passing through the lower half of the thoracic sympathetic chain; but they are not interrupted in the chain ganglions through which they pass.

The sympathetic nervous system receives additional fibers from the spinal cord by way of the visceral branches of the second, third and fourth sacral nerves, and from the brain through certain of the cranial nerves.

There are, then, these three streams of preganglionic visceral efferent fibers: (1) the cranial stream from the third, seventh, ninth and tenth cranial nerves; (2) the thoracicolumbar stream, from the thoracic and upper lumbar spinal nerves by way of the white rami, and (3) the sacral stream from the second, third and fourth sacral nerves. The cranial and sacral streams belong to what is commonly called the parasympathetic system.

Most of the sympathetic nerves contain, in addition to the fibers already discussed, also sensory fibers, which convey impulses from the viscera to the spinal cord. These sensory fibers have their cells of origin in the spinal ganglion and reach the sympathetic system by way of the white rami. Visceral reflexes therefore travel arcs of at least three neurons each. The impulses reach the spinal cord along visceral afferent fibers in the dorsal root and leave along preganglionic visceral efferent fibers in the ventral roots and white rami. These fibers end in sympathetic ganglions, and the impulses which they carry are relayed to involuntary muscle and glandular tissue by postganglionic fibers. The ganglions of the sympathetic trunk do not serve as reflex centers but only as relay stations in the conduction pathways from the spinal cord to the viscera.

The vasoconstrictor fibers arise in the central nervous system and leave the spinal cord as preganglionic fibers from the second thoracic to the second lumbar ganglia. These fibers are mixed with other autonomic fibers, such as sweat fibers, pilomotor fibers, oculopupillary fibers and accelerator fibers to the heart. They reach the sympathetic chain from the anterior roots by way of the rami communicantes. They end in one or the other of the ganglia, then leave as postganglionic fibers. Those fibers which supply the skin of the extremities communicate with the corresponding spinal nerve by way of the gray rami. Their distribution peripherally is that of the spinal nerve. Vasodilator fibers have not been demonstrated for all regions of the body. From the thoracic portion of the sympathetic system vasodilator fibers pass to the limbs by way of the branches of brachial and lumbar plexuses, but, as Howell [2] stated, the exact course of these fibers is not as yet entirely settled. The origin of these fibers from the sympathetic chain has not been demonstrated in the nerves of the limbs. They may follow the vasoconstrictors, or, as Bayliss' [3] work seems to show, vasodilator effects occur in afferent fibers which have the so-called antidromic action. The vasoconstrictor fibers for the limbs probably are distributed chiefly to the skin. Section of these fibers produces dilator effects, exerted largely in the arterioles. The skeletal muscles of the limbs, according to Gaskell,[4] receive both dilator and constrictor vasomotor fibers; the former, however, are in predominance. Metabolic substances play a rôle in producing vasodilatation in the muscles.

The caliber of the blood vessels is under a dual control: 1. The vasomotor fibers maintain the small arteries in a condition of tonus. 2. There is also a return of tonus after complete denervation of the arteries, which, as was shown long ago by Goltz and Ewald,[5] is capable of inducing variations in the caliber of the blood vessels.

As Howell [2] stated, there is an increased amount of evidence showing that the capillaries and veins are not fixed systems, and that they are also under the influence of local, chemical or special nerve fibers. Such fibers have been demonstrated for the portal and mesenteric veins. Krogh's [6] investigations on the capillaries of the frog showed that these

2. Howell, W. H.: Text-Book of Physiology for Medical Students and Physicians, ed. 10, Philadelphia, W. B. Saunders Company, 1927.

3. Bayliss, W. M.: On the Origin from the Spinal Cord of the Vasodilator Fibres of the Hind Limb and on the Nature of These Fibres, J. Physiol. **26**:173, 1901; Further Researches on Andromic Nerve Impulses, ibid. **28**:276, 1902.

4. Gaskell, W. H.: Further Researches on the Vasomotor Nerves of Ordinary Muscles, J. Physiol. **1**:262, 1878-1879.

5. Goltz and Ewald, quoted by Tigerstedt, Robert: A Text-Book of Human Physiology, New York, D. Appleton & Company, 1906.

6. Krogh, August: The Anatomy and Physiology of the Capillaries, New Haven, Yale University Press, 1922.

vessels receive vasoconstrictor fibers from the sympathetic system, thus maintaining the capillaries in a state of tonic contraction. According to Krogh, the vasomotor effects on the capillaries are exerted through Rouget's cells; there is no conclusive proof of the existence of these cells in the capillaries of the human being. The effects of metabolites of acid type and of histamine, in producing capillary dilatation, seem to be well established.

DEVELOPMENT OF SURGICAL METHODS †

Periarterial sympathectomy was suggested by Jaboulay [7] (1898) for trophic and gangrenous diseases of the extremities, but it was not until 1913, when Leriche became interested in this field, that the operation gained any prominence. Owing to Leriche's enthusiasm, many physicians and surgeons have employed the procedure and given varying reports on its success and failure. The hyperemia that developed following periarterial sympathectomy was at first explained on the grounds that the vasomotor fibers were centrifugal in distribution and consequently were sectioned during the periarterial sympathectomy. However, it was learned that similar hyperemia occurred on the opposite side on which operation had not been done. This gave rise to the belief that the hyperemia was more active than passive and that it resulted from sectioning of the centripetal ascending fibers.

The anatomic work of Kramer and Todd [8] and of Potts [9] on the innervation of the vessels of the extremities proved that with the exception of the subclavian and femoral arteries, which received sympathetic vasomotor fibers directly from the ganglia, the vasomotor innervation of the arteries and arterioles corresponded to the innervation of the somatic segments. Even though Leriche and Fontaine [10] have not been able to present anatomic proof, they still hold that some intramural nerve centers must exist in the arterial wall.

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† This section appeared in practically the form here given in Adson and Brown: The Treatment of Raynaud's Disease, Surg. Gynec. Obst. **48**:587 (May) 1929.

7. Jaboulay, quoted by Leriche, René: De l'élongation et de la section des nerfs périvasculaires dans certains syndromes douloureux d'origine artérielle et dans quelques troubles trophiques, Lyon chir. **10**:378, 1913.

8. Kramer, J. G., and Todd, T. W.: The Distribution of Nerves to the Arteries of the Arm with a Discussion of the Clinical Value of Results, Anat. Rec. **8**:243, 1914.

9. Potts, L. W.: The Distribution of Nerves to the Arteries of the Leg, Anat. Anz., 1914, p. 138.

10. Leriche, René, and Fontaine, René: Experimental and Clinical Contribution to the Question of the Innervation of the Vessels, Surg. Gynec. Obst. **47**: 631, 1928.

We have observed hyperthermia of the extremities in normal persons, and in patients with Raynaud's disease and thrombo-angiitis obliterans, following the febrile reaction after the intravenous injection of foreign protein; this may persist for several days. In some persons the reaction is so pronounced that injections of protein are prescribed as a therapeutic measure. We also have observed that following the administration of a general anesthetic to patients with vasoconstrictor disturbances there are hyperemia and increased surface temperature in extremities on which an operation has not been performed. It is our belief that these temporarily increased changes in blood flow which result from administration of protein are due to the heat-regulating mechanism which attempts to dispose of the increased body temperature, and further, that these temporary hyperthermic changes arising from periarterial sympathectomy, incomplete ramisectomy or ganglionectomy may be due to increased systemic temperatures following surgical procedures, but are more likely to be due to incomplete interruption of vasoconstrictor fibers. The more complete the division of postganglionic vasoconstrictor fibers, the more complete and permanent will be the results of the operation. In Raynaud's disease this is evidenced by the disappearance of the cyanosis and pain and permanently increased vasodilatation of the peripheral part, with the production of warm, comfortable, normal appearing hands and feet.

The work of Leriche and his followers has stimulated many surgeons to develop operative measures of a greater scope, attempting permanently to paralyze the vasoconstrictor nerves before they reenter the spinal nerves to be distributed to the arteries and arterioles. These operations have consisted of ganglionectomy, ramisection and section of the trunk. Jonnesco [11] was one of the first to advocate resection of the stellate [12] ganglion (lower cervical and first thoracic ganglia) for angina pectoris, but Brüning,[13] Hunter [14] and Royle,[15] Brown and

11. Jonnesco, Thomas: Traitement chirurgical de l'angine de poitrine par la résection du sympathique cervico-thoracique, Presse méd. **1**:193, 1921.

12. A question has been raised in regard to the use of the term "stellate" to indicate the lower cervical and first thoracic ganglia, in the human being. Dr. Charles W. Green has stated his belief that the use of the word stellate should be confined to the lower animals in which the lower cervical and first thoracic ganglia are frequently fused; this fusion is not common in human beings. Common usage by many workers, however, has led us to continue the use of the term "stellate ganglion."

13. Brüning, Fritz: Die operative Behandlung der Angina pectoris durch Extirpation des Halsbrustsympathicus und Bemerkungen über die operative Behandlung der abnormen Blutdrücksteigerung, Klin. Wchnschr. **2**:777, 1923.

14. Hunter, J. I.: The Influence of the Sympathetic Nervous System in the Genesis of the Rigidity of Striated Muscle in Spastic Paralysis, Surg. Gynec. Obst. **39**:721, 1924.

15. Royle, N. D.: The Treatment of Spastic Paralysis by Sympathetic Ramisection, Surg. Gynec. Obst. **39**:701, 1924.

Adson,[16] Diez,[17] and Davis and Kanavel [18] have been responsible for the renewal of our interest in the surgical possibilities in the treatment of vascular diseases of the vasoconstrictor type.

Royle,[15] in his report of Jan. 26, 1924, on the treatment of spastic paralysis by sympathetic ramisection, made this comment on examining a patient six hours after operation: "He noticed that the right leg, on the operated side, was brighter in color than the left, that it felt warmer and gave evidence of capillary dilatation, though he was unable to demonstrate any difference in temperature with an ordinary clinical thermometer."

Since May 20, 1924, the date of our first abdominal transperitoneal lumbar sympathetic ganglionectomy for spastic paralysis, we have observed marked hyperthermia verified by accurate quantitative studies. When the surface temperature of the feet remained elevated for months and gave evidence that it would remain so permanently, we concluded that we would be justified in trying the procedure on a patient with Raynaud's disease. This we did, on March 19, 1925, and reported our experience on June 20, 1925.[19] The relief of symptoms in that patient was so dramatic that we were almost afraid to believe our eyes. This patient and the others on whom we performed lumbar sympathetic ganglionectomy for Raynaud's disease continued to be relieved following the operation. We can confidently say, therefore, that they were completely cured of the disease as it affected the lower extremities.

Before proceeding with the description of surgical technic used by one of us (Adson) it might be of interest to review briefly the history of cervicothoracic ganglionectomy as carried out through the anterior approach.

Jonnesco [20] called attention to the fact that the operation, resection of the stellate ganglion, with or without resection of the middle and upper cervical ganglia, was first done, in 1896, for epilepsy and exoph-

16. Brown, G. E., and Adson, A. W.: Calorimetric Studies of Extremities Following Lumbar Sympathetic Ramisection and Ganglionectomy, Am. J. M. Sc. **170**:232, 1925.

17. Diez, J.: El tratamiento de las afecciones tróficas y gangrenosas de los niembros por la resección de las cadenas cérvico-torácica y lumbosacra del simpático, Prenza med. **12**:377, 1925-1926.

18. Davis, Loyal; and Kanaval, A. B.: Sympathectomy in Raynaud's Disease, Erythromelalgia and Other Vascular Diseases of the Extremities, Surg. Gynec. Obst. **42**:729, 1926.

19. Adson, A. W., and Brown, G. E.: Treatment of Raynaud's Disease by Lumbar Ramisection and Ganglionectomy and Perivascular Sympathetic Neurectomy of the Common Iliac, J. A. M. A. **84**:1908 (June 20) 1925.

20. Jonnesco, Thomas: Rescetia totală di bilaterală a simpaticulŭi cervical in cazurĭ de epilepsie si gusă exoftalmică, Romania med. **4**:479, 1896; translation in Centralbl. f. Chir. **24**:33, 1897.

thalmic goiter, and later, by other surgeons, for migraine and glaucoma. Jonnesco [11] followed a suggestion made by Frank [21] and performed his operation for the relief of angina pectoris. From that period until recently, it has been used by scores of surgeons for almost every conceivable ailment of the head, neck and upper extremities. The frequent alleviation of angina pectoris by resection of the cervicothoracic ganglia has justified its existence. The character of this article does not permit a review of the employment of surgical measures for angina pectoris. For Raynaud's disease and for scleroderma, Brüning,[22] in 1923, resected the cervicothoracic ganglia by the anterior approach. Davis and Kanavel, in 1926, carried out a similar procedure for Raynaud's disease of the upper extremities, with partial relief of the vasospastic disturbance.

In 1924, Royle [23] modified the Jonnesco operation, suggesting ganglionectomy and section of the trunk below the first thoracic ganglion by the anterior approach. We believe that his latest suggestion has offered the best anterior approach to the cervicothoracic ganglia. We agree with Royle also in his statement that operation in this surgical field is dangerous and that previous failures were due to incomplete operations. We disagree with him as to sectioning the thoracic trunk below the stellate ganglion, for Kuntz [24] showed that the second thoracic ganglion contributes gray fibers to the first thoracic spinal nerve, as well as to the second thoracic spinal nerve which often contributes to the lower trunk of the brachial plexus. Through the posterior intrathoracic approach, we were able at operation to substantiate Kuntz' observations.

All of these more or less partial or incomplete results in the treatment for vasoconstrictor disturbances of the upper extremities by resection of the so-called stellate ganglion convinced us that some other approach was necessary. Therefore, the problem that confronted us was to find a procedure that would permit complete removal of the first and second dorsal and lower cervical sympathetic ganglia and the intervening trunk, in order to break completely all sympathetic fibers to the subclavian and axillary arteries and to the brachial plexus. It appeared that the posterior approach was the logical procedure and was the method that we believed necessary when we failed in our first attempt to give relief

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21. Frank, Francois, quoted by Brüning (footnote 13).

22. Brüning, Fritz: Weitere Erfährungen über den Sympathicus, Klin. Wchnschr. **2**:1872, 1923.

23. Royle, N. D.: A New Operative Procedure in the Treatment of Spastic Paralysis and Its Experimental Basis, M. J. Australia **1**:77, 1924.

24. Kuntz, Albert: Distribution of Sympathetic Rami to the Brachial Plexus; Its Relation to Sympathectomy Affecting the Upper Extremity, Arch. Surg. **15**: 871 (Sept.) 1927.

in Raynaud's disease of the upper extremities by the anterior approach. The rami from the ninth, tenth, eleventh and twelfth dorsal ganglia were sectioned through a dorsal approach for a neuropathic condition of the abdomen by von Gaza [25] in 1924. In searching the medical literature for information concerning the exact anatomy of this field, our attention was called to Henry's [26] monograph on "Exposures of Long Bones and Other Surgical Methods" which contained an essay on an anatomic dissection of the cervicodorsal ganglion from the posterior approach, entitled "A New Method of Resecting the Left Cervicodorsal Ganglion of the Sympathetic in Angina Pectoris." [27] This evidence was sufficient to convince us that we could resect the second thoracic ganglion, the cervicothoracic and the intervening sympathetic trunk and thus completely interrupt all of the efferent fibers to the vessels of the arm as well as those to the head and neck. In our first case the procedure was divided into two operations: resection of the second thoracic ganglion, the cervicothoracic ganglion and the intervening sympathetic trunk on the right side was performed on July 31, 1928, and a similar operation was done on the left side on Sept. 11, 1928.[28]

As it was necessary to perform bilateral operations, Henry's [27] suggestions concerning skin and muscle flaps had to be modified. Furthermore, since we believed it necessary to include the second thoracic ganglia and rami, on account of Kuntz' [24] anatomic suggestion, we had to enlarge the scope of the operation to break all afferent impulses from the heart to the thoracic nerves. Only in this way could we expect to relieve the patient of all of the pain referred to the arms and thoracic wall. Cannon [29] showed that sensations of pain travel over afferent fibers to one or all of the five upper dorsal nerves.

SURGICAL TECHNIC

Removal of the Lumbar Ganglia.—The surgical procedure for the removal of the second, third and fourth lumbar ganglia and intervening trunk consists in a transperitoneal abdominal approach. The patient is placed in the Trendelenburg position, and the abdomen is opened in the median line from the symphysis to a

25. Von Gaza, W.: Ueber paravertebrale Neurektomie am Grenzstrange und paravertebrale Injektionstherapie. Ein beitrage zur Behandlung neurotisch-dysfunctioneller Krankheitszustände bauchinnerer Organe, Klin. Wchnschr. **3**: 525, 1924.

26. Henry, A. K.: Exposures of Long Bones and Other Surgical Methods, New York, William Wood & Company, 1927.

27. Henry, A. K.: A New Method of Resecting the Left Cervico-Dorsal Ganglion of the Sympathetic in Angina Pectoris, Irish J. M. Sc. **5**:152, 1924.

28. Adson, A. W., and Brown, G. E.: Raynaud's Disease of the Upper Extremities: Successful Treatment by Resection of the Sympathetic, Cervicothoracic and Second Thoracic Ganglions and the Intervening Trunk, J. A. M. A. **92**:444 (Feb. 9) 1929.

29. Cannon, W. B.: Personal communication.

point 7.5 cm. above the umbilicus. The intestines are permitted to fall into the upper part of the abdomen, and the left lumbar sympathetic chain is then exposed by reflecting the sigmoid and the descending colon to the median line, approaching the ganglia posterior to the descending colon and the sigmoid. The lumbar sympathetic ganglia on the right side are exposed by an incision in the posterior parietal peritoneum along the right lateral border of the abdominal vena cava. Further exposure of the lumbar sympathetic ganglia is accomplished by gentle elevation and rotation of the abdominal vena cava toward the median line.

Removal of the Upper Thoracic Ganglia.—The surgical procedure for the removal of the inferior cervical, first, and second thoracic ganglia and intervening sympathetic trunk consists in a cervicothoracic incision in the median line with a subsequent approach on each side of the spine. This approach to the cervicothoracic ganglion follows resection of the transverse process of the second thoracic vertebra in conjunction with resection of the second thoracic rib at the spinal articulation. Thus the mediastinum is entered by retracting the pleura and the lung laterally and forward, exposing the cervicothoracic ganglia which are to be removed. The surgeon must make sure to remove all of the second thoracic, first thoracic and inferior cervical ganglia with the intervening sympathetic trunk, effecting complete interruption of all efferent and afferent sympathetic impulses above the third thoracic ganglion.

EFFECTS OF GANGLIONECTOMY

Effects on the Vasomotor Nerves.—The vasomotor changes resulting from lumbar ganglionectomy have been studied, first by determining the variations in the surface temperature of the legs and feet by the thermocouples, and second by determining by means of the Stewart[30]-Kegerreis[31] calorimeter the amount of heat eliminated from the feet. We have, at present, no clinical method for accurately estimating the volume flow of blood through the limb. The methods available are those which give indirect data on the volume flow of blood through the part, as shown by Sheard.[32] The surface temperature measures the amount of heat in an isolated area of the skin, and gives information largely as to the state of the surface vessels. Surface temperature does not give exact information as to the changes occurring in the deeper vessels, although there is a close anatomic relationship between the deep and superficial circulation. It is certain that the vasomotor activity manifests itself in a larger degree in the vessels of the skin because of its sensitive heat-regulating mechanism. Likewise, measurements on the rates of heat loss give data dealing largely with the amount of blood in the surface circulation and with the vasomotor changes occurring in

30. Stewart, G. N.: Studies on the Circulation in Man: I. The Measurement of the Bloodflow in the Hands, Heart **3**:33, 1911-1912.

31. Kegerreis, Roy: Calorimetric Studies of Extremities: II. Experimental Apparatus and Procedures, J. Clin. Investigation **3**:357, 1926-1927.

32. Sheard, Charles: Calorimetric Studies of Extremities: I. Theory and Practice of Methods Applicable to Such Investigations, J. Clin. Investigation **3**: 327, 1926-1927.

the surface vessels of the entire hand or foot. These methods are of great value for comparative purposes, providing the studies are well controlled and carried out under comparable room or environmental temperature.[33]

Spastic Paraplegia.—Included in this group were twelve patients with spastic disturbances in the lower extremities and on whom lumbar ganglionectomy was performed in an attempt to modify the tonus of muscles of the legs. Surface temperature of the feet in these subjects before operation was not low. The peripheral vessels were patent, and as a rule abnormal or excessive vasoconstrictor activity was absent. The preoperative surface temperature of the foot varied from 25 to 29 C. (from 77 to 84.2 F.) (normal values). Table 1 indicates the pre-

TABLE 1.—*Changes in Surface Temperature* and in the Elimination of Heat After Lumbar Ganglionectomy in Spastic Paraplegia*

Case	Maximal Increase in Skin Temperature, Degrees C.		Heat Elimination, Small Calories Each Minute for Each Square Inch of Surface Area	
	Foot	Lower Part of Leg	Before Operation	After Operation
1	....	1.5	1.50	3.30
2	2.5	2.0	....	....
3	6.2	3.3	0.30	1.10
4	14.1	...	0.35	3.90
5	1.5	0.4	1.20	3.00
6	1.6	1.8	0.70	4.10
7	13.8	0.8	0.30	1.40
8	2.0	0.9	0.90	3.50
9	2.4	0.4	....	....
10	4.3	2.7	....	....
11	7.6	0.8	2.25	3.49
12	4.3	7.9	....	....
Average increase.....	5.2	2.0	0.94	2.90

* Final recordings made from fifteen to twenty-one days after operation.

operative and postoperative surface temperature. Following the operation there was an average increase in the surface temperature of the distal portion of the feet of 5.2 C. (9.4 F.) and in the lower leg of 2 C. (3.6 F.). The average rate of heat loss before operation was 0.94 small calories of heat eliminated each minute for each square inch of surface area. Following operation the average value was 2.9 calories, an increase of approximately 300 per cent. These studies were carried out from fifteen to twenty-one days after the operation. There were no significant changes in the color of the feet after the operation. Total loss of reflex sweating in the feet and lower part of the legs was a constant observation.

Vasospastic Disturbances in the Feet; Raynaud's Disease.—This section is based on six cases. Raynaud's disease is a symmetrical vaso-

33. Room temperature was maintained at between 23 and 26 C.

motor disturbance of the spastic type, affecting the acral areas and predominantly present in females. It is manifested by intermittent changes in the color and temperature of the extremity affected, with variations in the environmental temperature. The arteries of the extremities are patent, and pulsations are present in the usually palpable arteries. It is an intermittent disturbance, since temporary recovery follows exposure of the subject to increased temperature. The temperature of the skin of the extremities is usually low, although subject to wide variations, that is, poikilothermic. The stage of pallor indicates complete constriction of the terminal arterioles, capillaries and small venules.[34] The blood ceases to flow through the capillaries, which are visible because of the small segments of static blood retained in them. The degree of constriction and the amount of blood in the exposed

TABLE 2.—*Summary of the Changes in Surface Temperature and in the Rate of Heat Elimination in the Feet Following Lumbar Ganglionectomy in Raynaud's Disease*

	Maximal Increase in Skin Temperature, Degrees, C.			Heat Elimination, in Small Calories, Each Minute for Each Square Inch of Surface Area	
Case	Before Operation	After Operation	Increase	Before Operation	After Operation
1	31.2	35.5	4.2	0.51	0.85
2	22.1	36.6	14.5	0.44	1.32
3	23.9	36.1	12.2	0.94	1.04
4	22.2	33.2	11.0	1.21	0.69
5	19.9	32.7	12.8	0.23	1.17
6	15.0	33.2	18.2	0.39	1.03
Average values....	....	....	12.1	0.62	1.01

capillaries and small venules determine the visible color reaction. In the stage of cyanosis, partial relaxation of the arterioles and venules supervenes; blood is admitted slowly from the arterioles or by retrograde movement from the venules into the capillaries. The flow is extremely slow and irregular, and cessation is observed for long periods of time. The extremity becomes excessively cold. The rubor or recovery phase which occurs in some cases with higher environmental temperature represents relaxation of the arteriolar spasm, resumption of capillary flow and transformation of the cyanotic deoxygenated blood into that of the red oxygenated type of blood. The rubor or excessive red color of the extremity is due, then, to abnormally large exposure of red capillary blood flowing rapidly through an increased number of dilated capillaries and venules. The surface temperature is then high. It would

34. Brown, G. E.: The Skin Capillaries in Raynaud's Disease, Arch. Int. Med. **35**:56 (Jan.) 1925.

be expected *a priori* that interference of the vasomotor paths would produce complete alleviation of this disturbance by preventing spasm of the small arterioles.

The increase in the surface temperature of the distal parts of the feet following lumbar ganglionectomy was very high; the average for the group was 12 C. (15.6 F.). The preoperative temperature of the feet was very low, averaging only 22.4 C. (71.9 F.) under room temperatures of from 24 to 26 C. (from 75.2 to 78.8 F.). Following operation, increases were noted in the rates of heat elimination, averaging 0.39 calories each minute for each square inch of surface area, or 61 per cent. The relatively moderate increase in heat elimination

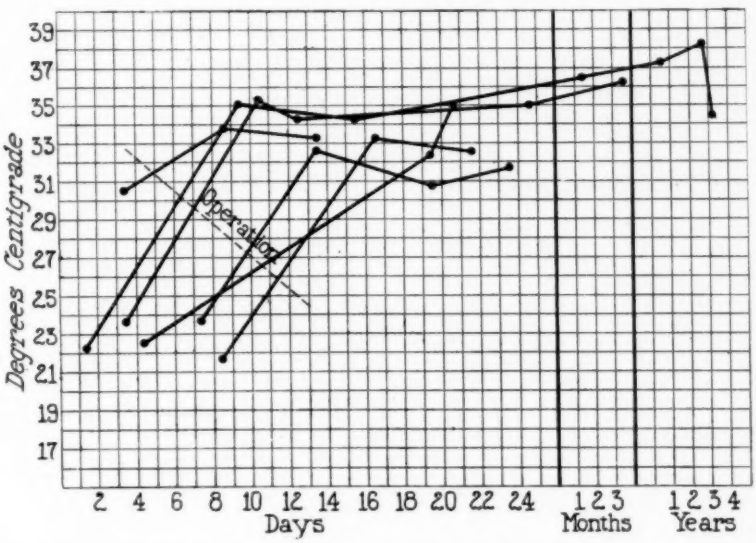

FIG. 1.—The surface temperature of the feet before and after lumbar ganglionectomy in a patient with Raynaud's disease. The initial point is an average of from two to six readings on different days before operation.

in the cases of Raynaud's disease is explained by the fact that many of the preoperative determinations were made on the extremity during periods when the feet were relatively warm. The increase and the duration of the increase in surface temperature are shown graphically in figure 1.

Residual Vasomotor Activity.—The amount of reflex vasomotor activity remaining in the arteries after operation, as studied by variations in the surface temperature, has been determined in several cases of Raynaud's disease (fig. 1).

After operation the range was very limited, varying from 1 to 4 C. (from 1.8 to 7.2 F.), much less than one would find in a normal

subject who had not been subjected to operation. The restricted fluctuation in the surface temperature after operation may be due to the fact that the few vasoconstrictor fibers remaining are sufficient to produce reflex effects, or to the natural or inherent tonus of the denervated vessels. The latter seems a more likely explanation, as with further lapse of time after operation there has been noticed a further decrease in the degree of changes occurring in the temperature of the skin. This is probably due to disuse atrophy which has been demonstrated in the walls of the arteries by Kerper and Collier [35] after lumbar ganglionectomy in experimental animals.

Thrombo-Angiitis Obliterans.—The rationale of carrying out lumbar ganglionectomy in cases of occlusive disease of the arteries affecting the extremities is based on the following clinical and physiologic observations: 1. In many cases of thrombo-angiitis obliterans, with closure of the main arteries, there are varying degrees of vasospastic disturbance. The color changes due to lowered environmental temperature are in some cases so striking as to lead frequently to an erroneous diagnosis of Raynaud's disease. This clinical observation leads to the conclusion that in some cases the collateral vessels maintaining the circulation of the extremities are subject to excessive vasospastic reactions. This is easily understood if the pathologic changes occurring in this disease are recalled, namely, marked inflammatory reaction in all coats of the arteries, especially in the adventitia or perivascular structures, and cellular thrombosis occluding segments of variable length. Afferent impulses, with the institution of vasoconstrictor reflexes, are undoubtedly initiated by the inflammatory process. 2. Further evidence of considerable vasomotor spasm is observed from the calorimetric and thermometric studies carried out on the extremities of some of these patients. The rate of heat elimination, as determined in the hand or foot calorimeter and as measured in small calories eliminated for each unit of surface area for each unit of time, is subject to variations similar to but less in degree than those observed in normal subjects or in subjects with functional vasospastic disturbances. It was assumed, therefore, that the diminished blood supply in some cases of thrombo-angiitis obliterans has a twofold basis: occlusion of the main arterial channels, and superimposed vasoconstriction of the collateral circulation.

In order to select the cases suitable for operation on the vasomotor nerves, a simple test was devised. The mouth temperature and surface temperature are taken to establish the normal for each patient under conditions of ordinary room temperature. Systemic fever is induced by

35. Kerper, A. H., and Collier, W. D.: Pathological Changes in Arteries Following Partial Denervation, Proc. Soc. Exper. Biol. & Med. **24**:493, 1927.

the intravenous injection of triple typhoid vaccine.[36] The mouth temperature and the surface temperature of the affected extremities are then determined simultaneously during the rise and fall of fever. In certain cases there are great increases in the surface temperature of the part, with small rises in the systemic temperature. A vasomotor index is determined in the following manner: The rise in the surface temperature minus the rise in systemic temperature represents approximately the temperature change in the skin due to vasomotor effects. This, divided by the increase in the blood temperature, gives a value which indicates that for every degree of rise in systemic temperature there is an increase in surface temperature due to shifting of additional

TABLE 3.—*Changes in Surface Temperature and Rate of Heat Elimination in the More Diseased Extremity Following Lumbar Ganglionectomy in Thrombo-Angiitis Obliterans*

Case	Increase in Surface Temperature of Toes, Degrees, C.		Heat Elimination, Small Calories, Each Minute for Each Square Inch of Surface Area	
	Minimal	Maximal	Before Operation	After Operation
21	4.2	5.0	1.10	5.00
22	0.6	6.0	0.70	1.50
23	0.8	7.6	0.40	0.70
24	1.3	5.3	0.45	0.70
25	2.7	5.6	0.90	1.60
26	2.3	2.3	0.70	0.60
27	4.7	8.0	0.38	0.98
28	1.9	7.6	0.99	0.62
29	9.8	10.7	0.58	0.61
30	...	3.3	0.83	0.69
31*	....	....	....	....
32	...	....	0.95	1.50
33	0.4	2.4	0.94	1.04
34	2.9	11.9	0.65	1.90
35	...	8.4	....	....
Average values.....	2.4	6.0	0.74	1.34

* Postoperative studies not carried out; double amputation performed.

blood to the surface, a vasomotor effect. After due consideration of the clinical aspects of the case we have advised operation arbitrarily in subjects who have had a vasomotor index of 2 or more. The ultimate validity of this criterion as a measure for selection of cases for operation can be determined only by carrying out the operation on a large number of patients. A comparison of the temperature curves from protein fever and those following operation shows fairly close approximation.

Fifteen patients with thrombo-angiitis obliterans affecting the lower extremities have undergone lumbar ganglionectomy. The increase in the surface temperature following this operation is quite different from that occurring in subjects with nonoccluded vessels. The increases are less; they lack uniformity in the different digits, contrary to that seen

36. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, J. A. M. A. **87**:379 (Aug. 7) 1926.

in cases of Raynaud's disease and in other conditions in which there are patent vessels. Huge increases in the rate of heat elimination are noted in some cases (fig. 2). We have noted healing of ulcers, relief from pain and marked improvement in many cases. The relief from pain following sympathetic ganglionectomy is frequently striking and cannot be entirely explained by the increased vasodilatation. After the febrile reaction that follows the administration of foreign protein in

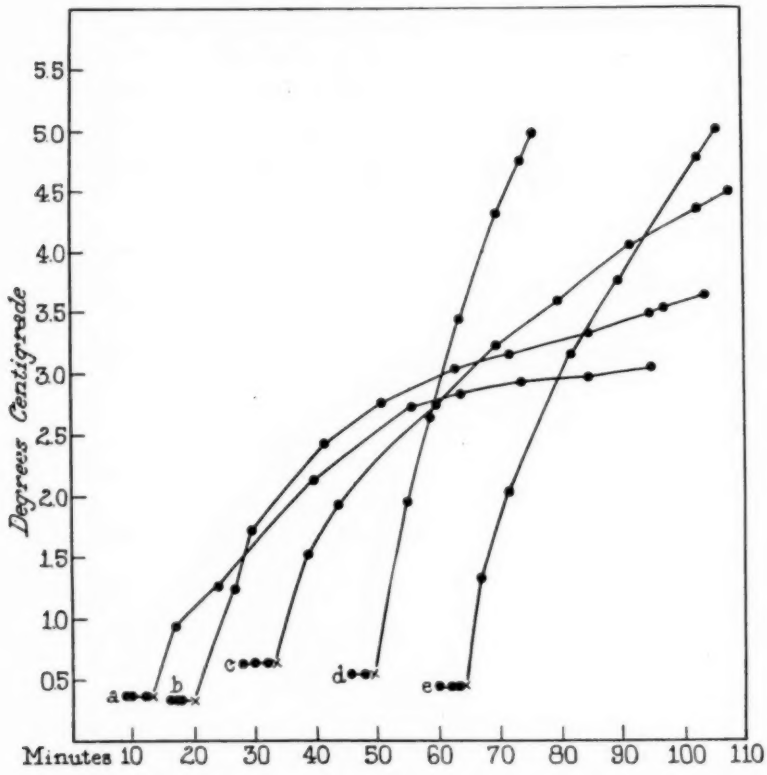

FIG. 2.—Increase in the rate of elimination of heat in the feet following lumbar ganglionectomy; *a* represents before operation, 0.69 calories; *b*, before operation, 1.10 calories; *c*, twelve weeks after operation, 1.68 calories, and *d*, six months after operation, 3.15 calories.

some cases, relief from the so-called "rest pain" or ulcer pain, may persist for several days, long after the phase of dilatation has passed. Probably, diminution of anoxemia in the tissues and riddance of irritating metabolites is an important factor in the effect. Fifteen patients have been operated on of whom three have undergone subsequent amputation of one leg; in two patients with gross gangrene of the feet at the time of operation, bilateral amputation subsequently was neces-

sary. The duration of vasodilatation obtained by operation in these cases is subject to the behavior of the primary disease. Progression of thrombosis in the arteries may occur regardless of operative measures, and large segments of arteries supplying collateral circulation may become thrombosed. In one case, one year after operation, there was thrombosis of both femoral arteries, probably extending into the iliac arteries, and sharp and sudden diminution of the blood supply to the feet occurred.

A woman, aged 34, with subacute arthritis, underwent lumbar ganglionectomy on June 6, 1926. This case was reported in detail by Rowntree and one of us (Adson),[37] who discussed the rationale of this

TABLE 4.—*In Subacute Arthritis Involving the Feet, Surface Temperature Before and After Lumbar Ganglionectomy* *

Date, 1925	Temperature, Degrees, C. Mouth	Room	Right Thigh	Right Leg	Right Foot	Right Toes	Left Thigh	Left Leg	Left Foot	Left Toes	Comment
5/19	36.6	24.0	....	....	....	....	34.8	34.0	35.0	25.6	
5/19	36.7	24.1	....	....	....	....	35.0	34.0	34.3	27.8	
5/20	37.0	23.0	....	....	....	....	....	33.0	33.9	26.0	
6/ 1	37.2	....	34.7	34.5	35.7	36.1	35.1	35.6	35.9	36.3	Lumbar ganglionectomy
6/ 2	37.4	....	36.5	36.1	35.8	36.4	....	....	....	....	....
6/ 3	37.7	....	....	....	....	....	36.1	35.3	35.9	35.5	Feet warm and dry
6/ 5	37.7	....	33.6	33.5	34.3	34.7	34.0	33.3	34.5	34.8	
6/ 7	36.6	....	35.2	34.6	34.0	34.5	34.8	34.5	34.8	34.8	
6/ 9	37.2	....	36.5	35.1	35.8	33.4	35.7	34.3	36.0	33.6	
6/10	37.2	....	35.7	34.3	36.0	33.6	36.5	35.1	35.8	33.4	
6/11	37.2	....	35.6	34.7	35.3	33.8	36.3	34.9	35.3	33.7	
6/14	36.8	....	33.7	33.7	34.7	33.3	34.7	34.4	35.5	34.0	
6/19	36.7	26.2	....	....	....	....	35.5	34.6	36.3	35.5	
8/ 4	37.0	28.0	....	....	....	....	35.7	35.7	33.0	36.0	Feet warm; no pain
8/ 9	37.0	22.7	....	....	....	....	....	35.5	35.0	36.0	Swelling disappeared
11/16	37.0	23.5	33.6	33.3	33.0	32.6	33.9	33.2	33.6	32.9	Weather cold
11/18	36.6	22.5	34.8	33.1	33.1	34.5	34.3	33.8	33.9	34.0	Feet warm and dry, no pain or arthritis in feet

* Case 13, woman, aged 34.

treatment. The preoperative surface temperature of the feet was fairly low; moderate acrocyanosis was present. Complete studies of temperature are shown in table 4. Diminution in vasodilatation was not found thirty months later. The clinical improvement was startling and was maintained.

Vessels of Amputated Limbs Following Lumbar Ganglionectomy.—Horton [38] determined in the amputated leg the effect of lumbar ganglio-

37. Adson, A. W.: Discussion, Proc. Staff Meet. Mayo Clin. **3**:333, 1928. Rowntree, L. G.: Result of Bilateral Sympathetic Ganglionectomy and Ramisectomy for Polyarthritis of the Lower Extremities, Proc. Staff Meet. Mayo Clin. **3**:333, 1928. Rowntree, L. G., and Adson, A. W.: Bilateral Lumbar Sympathetic Ganglionectomy and Ramisectomy for Polyarthritis of Lower Extremities, J. A. M. A. **88**:694 (March 5) 1927.

38. Horton, B. T.: A Study of Vessels of the Extremities by Injection of Mercury, Proc. Staff Meet. Mayo Clin. **3**:144, 1928.

nectomy on the capacity of the arterial tree. Several of his experiments are given:

CASE 1.—In a patient with thrombo-angiitis obliterans, lumbar ganglionectomy was performed. Ascending thrombosis of the femoral and iliac arteries then developed; sixty days after the lumbar ganglionectomy, amputation was necessary for gangrene of the distal half of the foot.

Weight of amputated leg	1,155 Gm.
Weight of leg plus mercury injected under pressure of 50 mm. of mercury with complete filling	1,500 Gm.
Content of arterial bed in grams of mercury filling ratio of 345/1155 or 30 per cent	345 Gm.

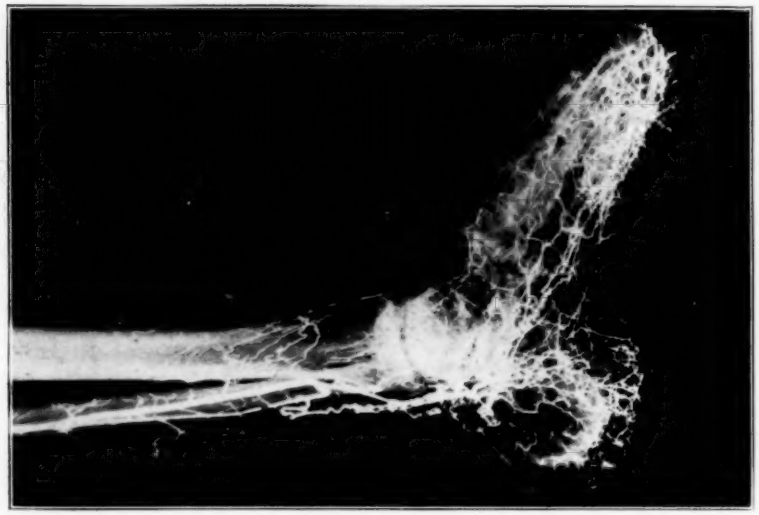

FIG. 3.—Leg amputated from a patient with thrombo-angiitis obliterans. The main arteries are closed and the collateral circulation is poor.

CASE 2 (control).—The leg was amputated from a patient with thrombo-angiitis obliterans without previous ganglionectomy. The level of amputation was comparable to that in case 1.

Weight of amputated leg	1,940 Gm.
Weight of leg plus mercury injected under pressure of 50 mm. of mercury with complete filling of the arterial bed	2,072 Gm.
Content of arterial bed in grams of mercury filling ratio of 132/1940 or 6.7 per cent	132 Gm.

Roentgenographic studies made by Horton after injection of mercury in the arterial bed, in amputated legs in cases of thrombo-angiitis obliterans, bring out in a striking manner further confirmation of vasodilator effects of ganglionectomy. In the amputated legs of subjects who have had lumbar ganglionectomy, the roentgenographic shadow of

the arteries containing mercury is wider and the collaterals are more prominent than in cases in which ganglionectomy has not been done. The mercury passes through the arterioles into capillary and venous beds, an observation which has never been made in limbs from control subjects (figs. 3 and 4). Further information was obtained from a pathologic study of the vessels in a subject who had undergone a bilateral lumbar ganglionectomy sixteen months previously. Bilateral amputation was performed for gangrene of both feet due to progressive, ascending thrombosis involving the iliac arteries (fig. 5). Sections were taken through the unoccluded dorsalis pedis artery, and then compared

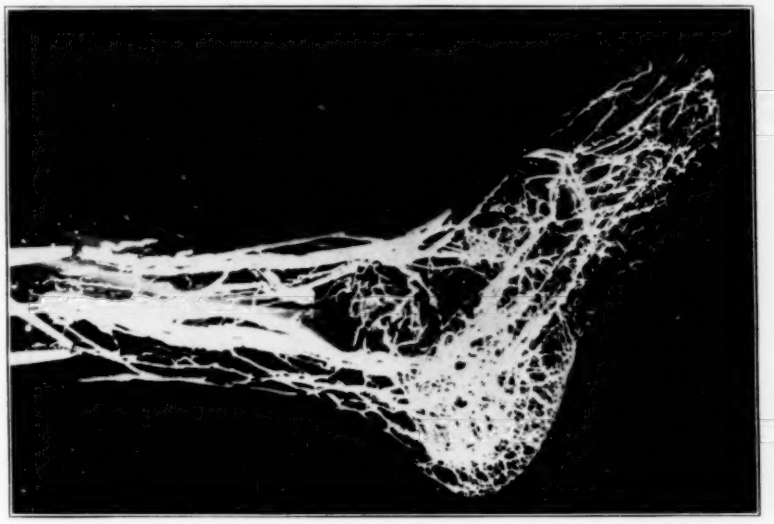

FIG. 4.—Leg amputated from a patient with thrombo-angiitis obliterans who had undergone lumbar ganglionectomy ten months previously. Collateral vessels show up heavily. There is marked filling of nondiseased segments of the arteries. Mercury passes into the veins.

with the dorsalis pedis artery of a control subject. The inference from this examination is that after lumbar ganglionectomy marked dilatation of the lumen of the arteries apparently exists with atrophy of the medial layer of the arterial wall. The ratio of vessel lumen to vessel wall is apparently increased 3.5:1 cm. (The normal ratio in arterioles, according to Anderson, Kernohan and Keith,[39] is 2:1).

The observations of Horton are in line with those of Kerper and Collier [35] who made histologic studies on the vessel changes in the goat

39. Anderson, E. W.; Kernohan, J. W., and Keith, N. M.: Histologic Studies of the Peripheral Arterioles in Ambulatory Patients with High Blood Pressure, Proc. Staff Meet. Mayo Clin. **3**:309, 1928.

and the cat after unilateral extirpation of the lumbar sympathetic trunk. In the vessels in the limb of the goat, in the distal portions of the denervated vascular tree, atrophy of the muscle fibers, apparent dilatation of the arterial lumen and edematous swelling in the muscle cells were noted, similar to the changes in the circular muscles found in vessels after reduced functional excitation, of disuse atrophy. These studies seem to give anatomic proof of the permanent dilative effects of extirpation of the lumbar ganglion and trunk with increased flow of blood in the denervated limbs.

Muscle Tonus after Lumbar Sympathetic Ganglionectomy.—The influence of the sympathetic nervous system on striated muscle and muscle tonus had been considered a problem of experimental physiology

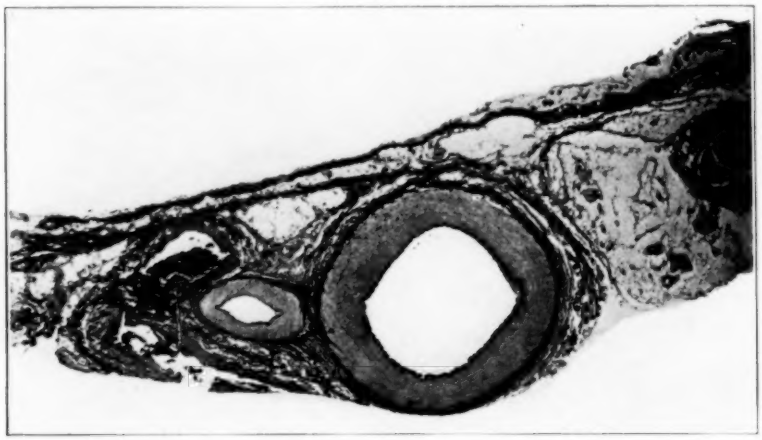

FIG. 5.—Cross-section of the dorsalis pedis artery six months after lumbar ganglionectomy.

until Royle [15] and Hunter [14] presented experimental and clinical data seemingly justifying a surgical procedure, "ramisection," which Royle carried out in spastic diseases.

Förster [40] advocated section of the dorsal roots in selected cases of spasticity, hoping to reduce the hyperactivity of muscles by interrupting the sensory reflexes. Stoeffel's [41] operation of fasciculectomy reduces the innervation to the spastic muscle and thus attempts to bring about a balance of antagonizing muscles.

Neither the Stoeffel nor the Förster operation offered a satisfactory solution in the treatment of spastic paralysis. Therefore we proceeded

40. Förster, quoted by Orth, Oscar: Ein Beitrag zur Förster'schen Operation, Zentralbl. f. Chir. **53**:598, 1926.

41. Stoeffel, quoted by Gill, A. B.: Stoeffel Operation for Spastic Paralysis, S. Clin. N. Amer. **6**:157, 1926.

to employ the surgical procedures suggested by Royle, keeping in mind that the anatomy and physiologic function of sympathetic innervated striated muscle was one of conjecture rather than established fact. In order to make the lumbar ramisection more effective in interrupting the efferent sympathetic fibers to the lumbosacral nerves, we resected the sympathetic trunk with the second, third and fourth ganglia. A simple section of the sympathetic trunk below the second lumbar ganglion might be sufficient. However, the distribution of the rami from the lumbar ganglia is irregular and not constant. Therefore, since complications have not arisen from the removal of ganglia we have been

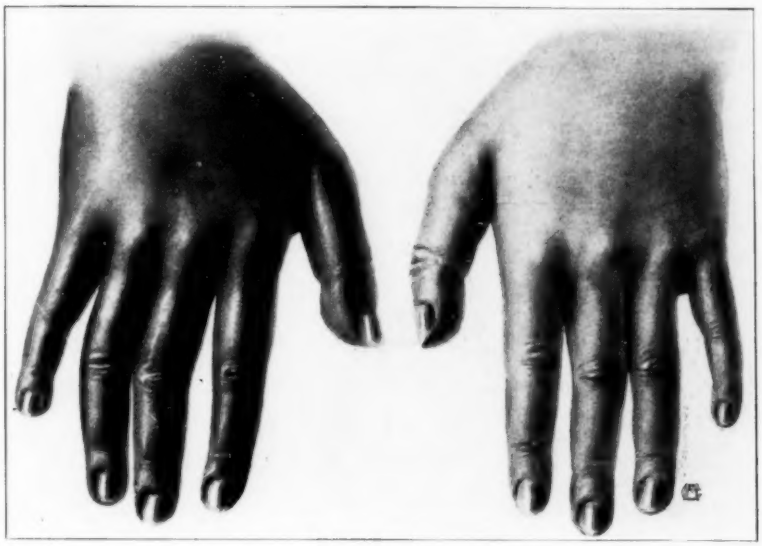

FIG. 6.—Appearance of the hands fifteen days after left thoracic sympathetic ganglionectomy in a case of Raynaud's disease.

persuaded to carry out the resection of the trunks and ganglia in order to make the operation more complete.

Our experience in spastic paralysis has shown that it is possible to reduce spasticity of the lower extremities in patients with cerebral diplegia, but that little is accomplished in cases in which the spasticity is due to unilateral cerebrovascular disturbances. We have accomplished nothing in spasticity resulting from disease or injury of the spinal cord, and have found that operation is of little or no value in patients with Parkinson's disease. Although operation may reduce the spasticity, it fails to alter the tremor or to interrupt the course of the disease. Therefore, the patient is dissatisfied with the result obtained. We have been unable, too, to alter the ataxia or the athetosis associated with

Little's disease. We are therefore employing the operation only in a rather select group of birth injuries, in children who are old enough to have sufficient mentality to cooperate in the program of reeducation. They must be free from athetosis and ataxia; they must be able to stand, although they may be too spastic to walk.

The operation should not be regarded as a cure-all for spasticity, but should be considered as a measure that may be employed in conjunction with other measures in order to improve the status of the patient. First to be employed are active and passive exercises, tendon stretching, plaster bandages, braces, tendon lengthening with subsequent support and exercises, Stoeffel's operation, etc.

The fact that the Royle operation has not been as effective on the lower as on the upper extremities would indicate that the operation is incomplete. Royle's more recent operation of section of the trunk

TABLE 5.—*In Various Diseases Involving the Arteries, Changes in Surface Temperature* and Rate of Elimination of Heat in the Fingers Following Bilateral Thoracic Ganglionectomy*

	Skin Temperature, Degrees, C. (Average of Several Readings)			Heat Elimination, Small Calories, Each Minute for Each Square Inch of Surface Area		
Case	Before Operation	After Operation	Increase	Before Operation	After Operation	Diagnosis
16	21.0	32.7	11.7	10	34	Raynaud's disease
19	23.3	32.8	9.5	22	80	Raynaud's disease
13	23.6	31.2	7.6	82	118	Arthritis of hands
36	24.9	28.0	3.1	70	140	Scleroderma
37	25.6	29.6	4.0	27	80	Scleroderma
38	23.3	30.2	6.9	47	63	Raynaud's disease
39	19.6	30.7	11.1	42	64	Raynaud's disease

* Average readings on all fingers for different days.

will be still more effective, no doubt, for conditions of the upper extremities. This can be further improved, we believe, by addition of the dorsal ganglionectomy suggested by us.

Removal of the Inferior Cervical Ganglion, the First and Second Thoracic Sympathetic Ganglia, and the Intervening Trunk; Effect on the Vessels.—This group comprises four cases of Raynaud's disease of the upper extremities, one case of subacute arthritis of the hands, and two cases of scleroderma affecting principally the hands.

Surface temperature in the hands sharply increased after operation in the four cases of Raynaud's disease. The average of many readings of the temperature of the skin of the fingers showed increases after operation of as much as 11.7 C. (21 F.). The average increase for the four cases was 9.8 C. (17.6 F.). The preoperative and postoperative observations were carried out at comparable room temperature. The patient with subacute arthritis (case 13) had fairly cold hands

before operation, as is fairly common in subjects with this disease. The increase in the skin temperature following operation, calculated from the average of many readings, was 7.6 C. (13.7 F.) on the skin of the digits. In all patients with vascular disease there were comparable increases in the rate of elimination of heat, varying from 70 to 300 per cent. These studies indicate that there was a large increase in the volume flow of blood, and this was borne out by the clinical improvement [42] (fig. 6). The thermometric studies were carried out from one to four months after operation; with this interval of time, vasodilatation had not diminished. In one case of Raynaud's disease, daily determination of the skin temperature of the hands, which was carried out over a period of years with great variations in the outdoor

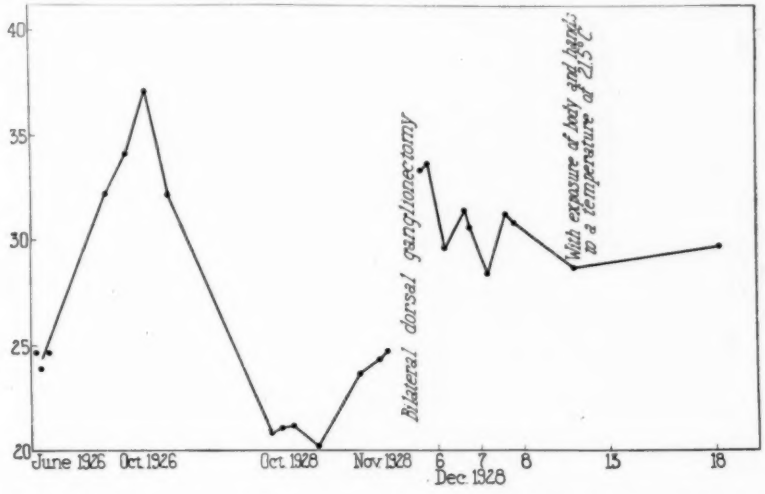

FIG. 7.—Vasomotor activity as studied by the surface temperature of the hands before and after dorsal ganglionectomy.

and room temperatures, showed huge changes in the skin temperature; following operation the residual vasomotor activity and the range in surface temperature of the diseased part were much less (fig. 7).

Vasodilatation of the vessels of the face was carefully studied in two cases after unilateral removal of the first and second thoracic sympathetic trunk and ganglia, the side on which operation had not been performed serving as a control. The first patient was examined with thermocouples, the surface temperature of the face and neck being determined at different descending levels, averaging 5 cm. apart.

42. Adson, A. W., and Brown, G. E.: The Treatment of Raynaud's Disease by Resection of the Upper Thoracic and Lumbar Sympathetic Ganglia and Trunks, Surg. Gynec. Obst., in press.

In a case of Raynaud's disease (case 19) determinations of surface temperature twenty-four days after excision of the first and second right thoracic ganglia were as shown in table 6.

TABLE 6.—*Surface Temperature Twenty-Four Days After Excision of the Right First and Second Thoracic Ganglia in Case of Raynaud's Disease*

Anterior Surface	Left Side, Degrees, C.	Right Side, Degrees, C.
Forehead	33.0	34.0
Cheek	34.2	34.4
Lower jaw	33.9	34.3
Neck	33.6	34.1
Subclavicular area	34.0	32.7
Nipple line	34.0	33.4
Costal margin	34.0	33.7
Posterior Surface		
Occiput	32.0	33.1
Lower part of neck	33.1	33.6
Interscapular area	32.9	33.3
Lower scapular area	33.0	33.3

TABLE 7.—*Surface Temperature Eight and Nine Days After Removal of Left First and Second Thoracic Ganglia in Case of Scleroderma*

Area	Left Side, Degrees, C.	Right Side, Degrees, C.
Forehead	32.2	31.1
Cheek	31.9	31.3
Neck	31.6	31.9
Anterior part of chest	32.7	32.0

In a case of scleroderma of the hands and face (case 36), determinations of surface temperature eight and nine days after removal of the left first and second thoracic ganglia were as shown in table 7.

Effect on the Surface Capillaries.—As was noted previously, vasomotor fibers have not been demonstrated in the capillaries in the skin of human beings. There is considerable collateral evidence to indicate that such fibers may be there. The pallor in the skin induced by psychic effects and the attacks of blanching in the extremities, noted in subjects with vasospastic disturbances, are a commonplace evidence that neurogenic control of the minute surface vessels exists. Reflex dilatation of these vessels in certain areas frequently is observed. Besides the probable neurogenic basis concerned with behavior of the smallest vessels, various metabolites and perhaps hormonal substances are involved. In cases of Raynaud's disease the effect that section of the vasomotor nerves has on the surface capillaries is of extreme interest in this connection. Visual information can be obtained by use of the microscope and adequate illumination, as first used by Lombard.[43] The following observations have been made:

43. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, Am. J. Physiol. **29**:335, 1911-1912.

In cases of Raynaud's disease, in which vasoconstrictive phenomena of the acral areas are the basic disturbance, there is loss of capillary tonus when this condition has persisted for a period of time. The hands are continually cyanotic and recovery to the stage of rubor and resumption of active capillary circulation become increasingly difficult. The appearance of the nailfold capillaries is characteristic;[36] there are large dilated loops and dilated venules containing static cyanotic blood due to a low content of oxygen. When movement of capillary blood occurs the flow is slow; the blood enters the loops in segments, lending a broken or segmented appearance to the loops. Following resection of thoracic ganglia, the hands become warm, maintain a fairly normal pink color and the reflex changes in color of the skin are abolished or are greatly impaired. The capillary loops are narrower, the outlines are more clearly defined, and a lesser number are in evidence. The

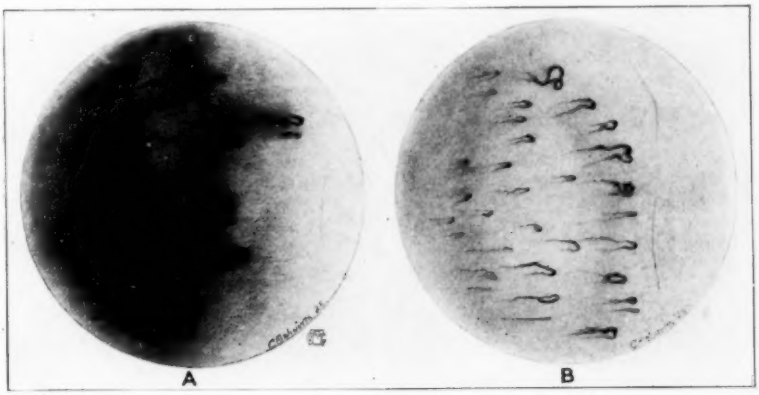

FIG. 8.—*A*, capillaries of the nailfold before operation. Venules and capillaries are dilated. The capillary blood is stationary or intermittent, giving a cyanotic color to the skin. *B*, capillaries of the nailfold after operation. The capillary loops are narrower. Venous stasis has disappeared. Capillary flow is rapid and uniform, giving the skin a normal pink color.

flow is rapid and the blood is red. The venules are narrower or become invisible on microscopic inspection (fig. 8.) In subjects without vasomotor disturbances, such as those with spastic paraplegia, observations of the skin on the feet after lumbar ganglionectomy did not reveal change in color, and demonstrable variations were not noted in the capillaries.

There has not been evidence in any case of this series, at least with methods available, to indicate that capillary dilatation follows interruption of the vasomotor nerves. In one case of Raynaud's disease it was noted that after operation complete recovery of capillary tonus did not follow. The tips of the fingers, although warm, remained red;

this was accentuated by the dependent position, and the normal color was obtained by elevation. The capillaries remained dilated but in a less degree than before operation. The flow in the loops was rapid and uninterrupted, indicating abeyance of the arteriolar spasm.

Comment.—These observations lend support to the belief that factors other than those of nervous origin are of importance in the maintenance of capillary tonus, that tonus is restored in some degree by blocking the vasoconstrictor fibers and that probably this restoration is brought about by the production of an uninterrupted flow of arterial blood through the capillary loops. The effect of stasis in the capillary blood, with high concentration of carbon dioxide or perhaps of other acid metabolites, seems more effective in modifying tonus in the surface capillaries than the neurogenic factor. As tonus of capillaries may not be com-

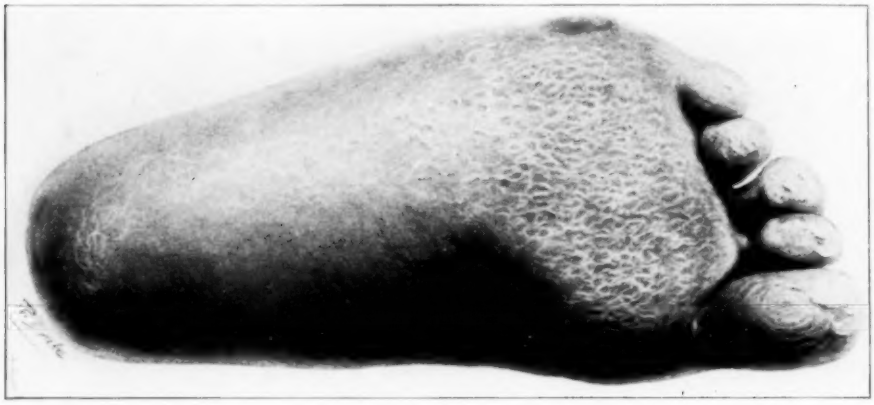

Fig. 9.—Skin of the palmar surface of the foot following lumbar ganglionectomy.

pletely restored after operation it seems likely that permanent loss of tonus occurs when the vasoconstrictive disease has been present for long periods of time.

Interference with Sweating Following Lumbar and Thoracic Ganglionectomy.—The anatomic pathways of the sweat fibers for the posterior extremities in the cat have been worked out with great care by Langley.[44] He found that the fibers leave the spinal cord chiefly in the first and second lumbar nerves, enter the sympathetic chain and emerge from this in the postganglionic fibers which pass from the sixth lumbar to the second sacral ganglia. They then join the nerves comprising the sciatic plexus. For the anterior extremities the fibers leave the spinal cord in the thoracic nerves from the fourth to the tenth, enter the

44. Langley, J. N.: On the Course and Connections of the Secretory Fibres Supplying the Sweat Glands of the Feet of the Cat, J. Physiol. **12**:347, 1891.

sympathetic chain and pass upward to the first thoracic ganglion where they are continued as postganglionic fibers and communicate with the nerves forming the brachial plexus. It has been shown that the sweat nerves are genuine secretory nerves and that their action cannot be explained merely as causing a direct variation in the blood flow.

It was found that after lumbar ganglionectomy, perspiration, as determined by the palpating hand, disappeared in the feet and lower part of the legs to a variable level at or just below the knee. The driest areas occurred in the feet. In one case of spastic paraplegia, desiccation in the soles of the feet was extreme, producing a condition similar to that observed in chronic icthyosis (fig. 9). Disagreeable or untoward symptoms did not result from the disappearance of sweating except in one case of Raynaud's disease with sclerodermal changes in the skin of the feet; in this case, the inhibition of sweating and dryness of the skin produced small fissures over the malleoli. Complete

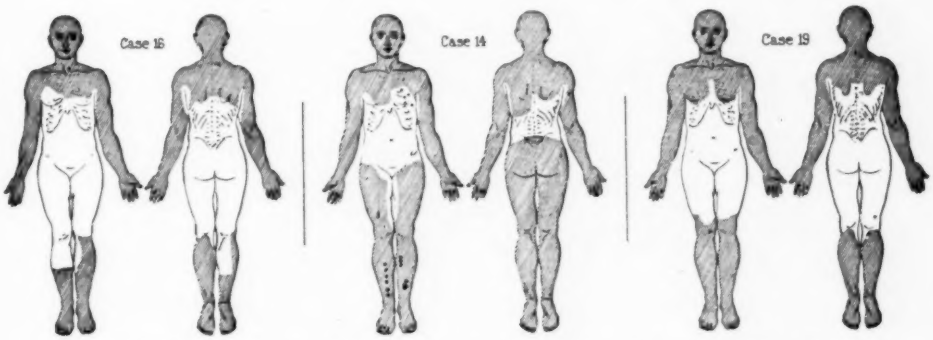

Fig. 10.—Shaded areas indicate absence of sweating under conditions of high environmental temperature. The black dots in case 14 indicate isolated droplets of sweat.

studies were carried out in three cases to determine the exact levels for the interference with sweating. The studies were made with cobalt blue test papers and by means of a miniature galvanic cell applied to the skin; the resultant current which was set up in the presence of electrolytes in solution (sweat) could be read by the swing of the galvanometer. The patients were placed in a heated chamber, for forty minutes at a temperature varying from 45 to 46 C. (from 113 to 114.8 F.), or until such time as a visible sweating occurred over the abdomen. In the three cases in which lumbar ganglionectomy had been performed, respectively, one month, eighteen months and thirty-six months previously (fig. 10), there was considerable variation in the line of demarcation between areas in which there was sweating and areas in which sweating was absent. In case 16, in which the operation had been performed three years previously, the upper limit of the area in which

sweating was absent was lower on the right leg than on the left. When compared with the mapping in case 14 in which operation had been performed eighteen months previously, considerable difference was observed. In case 14 the dry areas extended to Poupart's ligament anteriorly and to the iliac crest posteriorly. There was an area along the mesial surfaces of the thigh in which sweating was present. Also, in this case isolated droplets of sweat could be detected in the dry skin of the lower extremities. In case 19, in which operation had been performed one month previously, interference with sweating was noted up to a line about 5 cm. above the knees anteriorly and to the level of the popliteal space posteriorly.

The areas in which sweating was absent in the upper extremities in the three subjects were found to be more uniform than those of the lower extremities. Roughly, the upper areas included the head and neck, extending down to the nipple anteriorly and to the lower border of the scapula posteriorly. The axillas and mesial surfaces of the upper parts of the arms were moist. The driest areas were on the hands, although excessive scaling, as noted on the feet, was not observed. The loss of sweating is probably permanent; at least it has persisted in case 16 up to three years after operation. In patients who have had dorsal and lumbar operations, the total area of the body surface over which there is sweating is markedly reduced. This raises the question whether the heat-regulating mechanism of the body is not impaired. Some information has been obtained on this point by following the systemic temperature of one of these subjects while in the heating chamber. The systemic temperature reached 99.5 F. when the temperature of the chamber was increased to 45 C., the equivalent of 113 F. Prolonged observations on the effects of summer temperature and active exercise will be necessary to determine this point. It is probable that this reduction in area of the body over which sweating occurs may produce untoward symptoms under abnormal environmental conditions.

Pilocarpine was given to four subjects after lumbar and dorsal ganglionectomy, and visible sweating was induced in the usually dry areas. This is evidence that degeneration of the sympathetic nerve-endings in the sweat glands had not occurred within the periods of postoperative observation.

Pilomotor Reactions.—It is generally assumed that the pilomotor fibers follow the same general course as the secretory fibers to the sweat glands. In these patients it was noticed that there was loss of the pilomotor reaction in all patients who had undergone lumbar ganglionectomy. In extreme cases the loss persisted up to three years. The zone of demarcation could not be accurately determined by inspection, for the dryness of the skin sometimes seriously interfered with

visualization of the pilomotor reaction. Roughly, in the lower extremities the areas of absent pilomotor reactions were approximately the same as those in which sweating was absent. In the upper extremities, the pilomotor reflex was absent in the arms, but was present in variable degree over the shoulders and back.

THE ACCELERATOR RESPONSE OF THE HEART AFTER EXCISION OF THE INFERIOR CERVICAL AND FIRST AND SECOND THORACIC GANGLIA

The accelerator nerves to the heart, as summarized by Howell,[2] arise from the spinal cord in the anterior roots of the third, fourth and fifth spinal nerves; they may emerge also in the first and second thoracic nerves. Variations are found in different animals. These accelerator nerves pass to the first thoracic ganglion as the preganglionic fibers or white rami and then, by way of the annulus of Vieussens, to the inferior cervical ganglion. Some fibers end in synapses in the first thoracic and others in the inferior cervical ganglion. None is found above the inferior cervical ganglion. Several investigators have maintained that accelerator fibers are present in the vagus. It was shown by Hunt [45] that the accelerators to the heart maintain it in a state of tonic activity and that cutting these nerves in animals produces a decrease in the rate of the heart. The inhibitory fibers in the vagus create a balance between two antagonistic actions. This, no doubt, makes the heart more responsive to reflex adjustments.

Studies on the cardiac response to exercise were carried out in three patients after excision of the inferior cervical and first and second thoracic ganglia.

CASE 19.—In a patient with Raynaud's disease, twenty-one days after removal of the right first and second thoracic ganglia the blood pressure in millimeters of mercury, with the patient at rest, was from 108 to 110 systolic and 70 diastolic; the pulse rate was, at various times, 81, 86 and 84. Sixty seconds after the patient had climbed three flights of stairs, the blood pressure readings were as follows: systolic, 110; diastolic, 70; and again, systolic, 108; diastolic, 72. The pulse rate at the time of these readings was 89 and 84, respectively. After the patient hopped on one foot thirty times, the blood pressure was 110 systolic and 70 diastolic, and the pulse rate was 84.

Thirty days after right thoracic ganglionectomy, the blood pressure with the patient at rest was 110 systolic and from 76 to 80 diastolic; three readings of the cardiac rate, taken at this time, were 90, 93 and 90. The patient was required to hop fifty times on one foot. Blood pressure readings were: after thirty seconds, 98 systolic and 92 diastolic; after sixty seconds, 98 systolic and 88 diastolic; after 120 seconds, 100 systolic and 82 diastolic; corresponding cardiac rates were 102,

45. Hunt, Reid: Direct and Reflex Acceleration of the Mammalian Heart with Some Observations on the Relations of the Inhibitory and Accelerator Nerves, Am. J. Physiol. **2**:395, 1899.

98 and 94. Cardiac rates were taken also after 180 seconds and after 240 seconds; these readings were 89 and 81, respectively.

Sixty-six days after right dorsal ganglionectomy, and twenty-four days after removal of the first and second, and inferior cervical thoracic ganglia on the left side, with the patient at rest, blood pressure readings were 112 systolic and 70 diastolic, and again, 114 systolic and 72 diastolic. The cardiac rates taken four times at the same examination read 68, 68, 76 and 76. After the patient had walked up three flights of stairs, the cardiac rates were 132, 124, 108 and 100. At the end of two and a half minutes the rate had dropped to 84.

Forty-one days after thoracic and cervical operation, with the patient at rest, blood pressure readings were 106 systolic and 60 diastolic, and again, 106 systolic and 68 diastolic. Three readings of the cardiac rate at this time were 62, 66 and 70.

After the patient had walked up three flights of stairs, blood pressure readings were as follows: at the end of one minute, 115 systolic, 74 diastolic, and a cardiac rate of 110; at the end of two minutes, 108 systolic, 68 diastolic, and a cardiac rate of 66. At the end of eight minutes, the cardiac rate was 70.

The cardiac response in this patient indicates that after removal of the first and second thoracic ganglia on the right side there was moderate or slight acceleration of the heart following moderate grades of exercise. However, when twenty-four days had elapsed after the operation had been carried out on both right and left sides and when more severe exercise had been taken, rapid acceleration of the cardiac rate was noted although the reaction was subject to variation. Abnormal symptoms or signs did not appear following these exercises.

Case 13.—A woman, aged 34, with subacute arthritis, underwent resection of a lumbar ganglion eighteen months previously and bilateral resection of the first and second thoracic and inferior cervical ganglia twenty-four days previously. With the patient at rest, blood pressure readings were 156 systolic and 100 diastolic; the cardiac rate was 64. After the patient had walked up three flights of stairs, the readings were as follows: 170 systolic and 106 diastolic, and a cardiac rate of 104; at the end of one minute, 174 systolic and 108 diastolic, and a cardiac rate of 72; at the end of two minutes, 166 systolic and 100 diastolic, and a cardiac rate of 64; at the end of three minutes, 160 systolic and 100 diastolic, and a cardiac rate of 64; at the end of four minutes, 160 systolic and 100 diastolic, and a cardiac rate of 66, and at the end of five minutes, 156 systolic and 100 diastolic, and a cardiac rate of 68. Half an hour after the last observation, 0.6 mg. of atropine was given by mouth; the mouth was dry and the pupils were dilated. With the patient at rest, blood pressure readings were 150 systolic and 100 diastolic, and the cardiac rate was 72. After the patient had walked up three flights of stairs, the readings were: 175 systolic and 112 diastolic, and a cardiac rate of 100; at the end of one minute, 168 systolic and 116 diastolic, and a cardiac rate of 70; at the end of two minutes, 160 systolic and 104 diastolic, and a cardiac rate of 76, and at the end of three minutes, 162 systolic and 104 diastolic, and a cardiac rate of 74.

Twenty-seven days after operation, with the patient standing, the pulse rate was from 79 to 80. After the patient had climbed three flights of stairs, the pulse rate was 106; two minutes later it was 80.

The accelerator effect of exercise was preserved in this patient although the response was less pronounced than in the normal controls. Abnormal subjective symptoms were not complained of, and dyspnea on exertion was of the usual type. Following mild atropinization, acceleration was present in a similar degree.

CASE 16.—In a woman, aged 25, with Raynaud's disease, thirty months had elapsed after bilateral cervical ganglionectomy, with removal of all or cervical portions of the stellate and middle cervical ganglia through the anterior approach. The operation had been followed by bilateral Horner's syndrome, but without relief to the vasospastic disturbance of the hands. With the patient at rest, blood pressure readings were 108 systolic and 70 diastolic, and the cardiac rate was 84. After the patient had climbed three flights of stairs, the readings were: 135 systolic and 75 diastolic, and a cardiac rate of 148, and at the end of two minutes, 112 systolic and 74 diastolic, and a cardiac rate of 64.

Thirty-seven days after bilateral removal of the first and second thoracic ganglia, with the patient at rest, the blood pressure readings were 100 systolic and 60 diastolic, and the cardiac rate was 70. After the patient had climbed three flights of stairs, the readings were as follows: 118 systolic and 78 diastolic, and a cardiac rate of 106, and at the end of one minute, 100 systolic and 58 diastolic, and a cardiac rate of 76. On another day, the cardiac rate was as follows: with the patient at rest, 60; with the patient standing, 60; immediately after rapid walking, 80, and thirty seconds later, 64.

Twenty minutes after 2 mg. of atropine was given by mouth, the mouth was excessively dry and the cardiac rate was 76. The cardiac rate was then taken after two minutes, three minutes, five minutes and nine minutes; these readings, respectively, were 80, 92, 98 and 100. After rapid walking, the cardiac rate was 104; half a minute later it was 100; after two minutes it was 92, and after four minutes, 76.

The data in this case give evidence that the cardiac response to exercise was preserved for two and a half years after cervical ganglionectomy in which the inferior and middle cervical ganglia were removed, that after removal of the first and second dorsal ganglia the accelerator response to exercise was preserved but perhaps was less effective, and that following the administration of atropine, acceleration of the heart was pronounced.

This patient complained of palpitation of the heart while at rest following cervical ganglionectomy, and during the ensuing period of two years, signs and symptoms of irritable heart developed. According to the patient's statement, during periods of palpitation the rate of the heart was somewhat elevated. After the dorsal sympathetic ganglionectomy, palpitation still persisted in a mild degree but with a normal or slowed rate. Electrocardiographic tracings did not reveal significant changes before and after dorsal ganglionectomy.

Comment.—These studies are of interest from several standpoints: 1. The patients were young and were not suspected of having organic disease of the heart; the observations made cannot be compared with those made in older subjects with angina pectoris. 2. As one of us (A. W. A.) has pointed out, complete removal of the cervicodorsal, or what is known as the stellate, ganglion is difficult from the anterior approach. The thoracic portion may be separate from the cervical portion; therefore, it remains problematic after operation by the anterior approach whether extirpation has been complete. By the posterior approach, the first and second dorsal ganglia, with the sympathetic trunk, are removed without question. Following this type of operation, the cardiac response seems to show slight impairment of acceleration

in certain subjects; this is not uniform and may be a postoperative exhaustion effect. Evidence was not obtained to indicate that organic changes or serious functional disturbance of the heart are sequelae. Some information on the late effects of cervical ganglionectomy is furnished in case 16, in which studies three years after operation show a fairly normal acceleration of the heart. Further and more complete studies must be carried out. Brüning could not find predominant action of the antagonist to the heart by bilateral removal of the stellate ganglia. Jonnesco and Ionescu [46] have shown that following bilateral extirpation of the stellate ganglia in man, the heart retains the ability of accommodation to the usual demands of age. They concluded that the accelerator nerves in man are not vital nerves. Cannon, Lewis and Britton [47] have demonstrated that with extirpation of the hitherto recognized nerves reaching to the cat's heart, acceleration of the heart is still preserved. They presented evidence to show that accessory accelerator fibers from upper thoracic ganglia, below the stellate, mediate the faster beat. Removal of these maintains the cardiac rate within a fairly narrow range. A more recent anatomic study by Ionescu and Enaschescu [48] has demonstrated that efferent nerves leave the second to the fifth thoracic ganglia and pass to the heart. This would indicate that cardiac acceleration may be retained after extirpation of the stellate ganglion since only a part of the sympathetic nerve fibers to the heart are removed.

In a communication from C. W. Greene, he stated:

> I have experimental animal data that indicate that the heart rate may be influenced both by stimulation, that is, slowing, and by inhibition of the vagus reflexes, that is, acceleration.

The information obtained in case 16, with adequate atropinization, would show that with the effect of the vagus probably completely eliminated, cardiac acceleration still occurs. This further suggests the existence of accessory cardiac efferent nerves.

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46. Jonnesco, Thoma; and Ionescu, Dimitrie: Experimentelle und klinische Untersuchungen über den funktionellen Zustand des Herzens und der Gefässe nach Extirpation des cervicothorakalen Sympathicusstranges, Ztschr. f. d. ges. exper. Med. **48**:516, 1925-1926.

47. Cannon, W. B.; Lewis, J. T., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands. XVII. A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, with Evidence for Accessory Accelerator Fibers from the Thoracic Sympathetic Chain, Am. J. Physiol. **77**: 326, 1926.

48. Ionescu, Dimitrie; and Enaschescu, Marin: Untersuchungen bei Säugetieren und beim Menschen über die aus dem Brustgrenzstrang des Sympathicus unterhalb des Ganglion stellatum entsprungenen Herznerven; Nervi cardiac thoracales, Ztschr. f. Anat. (Abt. 1) **85**:476, 1928.

The following personal communication has been received from Kuntz:

We have traced nerves from the thoracic sympathetic trunk into the cardiac plexuses in not less than six cadavers. We find rami of considerable size arising from the third and fourth thoracic sympathetic ganglions. These rami enter the superficial and deep cardiac plexuses. To what extent the fibers of these small rami are distributed to the heart cannot be stated since the pulmonary plexuses are continuous with the deep cardiac plexus. We are not prepared to say at present whether these nerves are constant in man, although I rather expect that they will be found to be fairly constant.[49]

BERNARD-HORNER'S SYNDROME FOLLOWING THORACIC GANGLIONECTOMY

Following extirpation of the inferior cervical or cervicodorsal ganglia or section of the intervening sympathetic innervation of the eye and eyelids, characteristic changes in the pupil and eyelid occur. Dupry,[50] in 1815, after removal of the superior cervical ganglion in horses, noted vascular injection of the conjunctiva and increased temperature in the ear. Bernard,[51] in 1851, was the first to note increased vascularity and elevated surface temperature of the face after resection of the cervical sympathetic cord in rabbits, thus discovering the vasomotor nerves. In 1869, Horner[52] called attention to partial ptosis, contraction of the pupil and elevation of the surface temperature of the face in a patient; he ascribed the condition to a lesion of the sympathetic nerves of the neck on the affected side. Since then, these oculopupillary phenomena have been known as Horner's syndrome. The ocular changes occur immediately after section of the cervical sympathetic cord or resection of the ganglia. The pupil is small, does not react to cocaine or atropine, but retains the reflexes to light and in accommodation; there is narrowing of the palpebral fissure with apparent enophthalmos. Movements of the eyelids are not impaired, and the partial ptosis is ascribed to loss of tonus in the nonstriped muscle fibers. Various gradations in the intensity of this interesting syndrome are observed. Associated with the ocular phenomena is increased surface temperature of the face on the side on which operation has been performed. Jaboulay and

49. This work was reported by A. Kuntz, A. H. Kerper and A. Morehouse at the meeting of the American Association of Anatomists, Rochester, N. Y., from March 28 to 30, 1929.

50. Dupry, quoted in review of Claude Bernard and his physiological works, Am. J. M. Sc. **76**:161, 1878.

51. Bernard, Claude: in Foster, Michael: Masters of Medicine; Claude Bernard, London, T. Fischers, 1899.

52. Horner, F.: Ueber eine Form von Ptosis, Klin. Monatsbl. f. Augenh. **7**: 193, 1869.

Ionescu [53] also noted dilatation of the retinal vessels. Leriche and Fontaine [54] have clearly defined the severity and completeness of the oculopupillary syndrome following resection of the cervical sympathetic cord at different levels. They concluded that the sympathetic fibers to the eye leave the sympathetic cord just above the first thoracic ganglion and follow the vessels entering the cranium. Section of the sympathetic cord at the level of the superior cervical ganglion produces less intense changes than section at the level of the stellate ganglion.

In seven cases, after extirpation of the upper thoracic ganglia, Horner's syndrome was evident immediately after operation. The persistence and completeness of the reaction varied considerably in each case. In case 19, one of Raynaud's disease, the syndrome was fairly well marked after resection of the right first and second thoracic ganglia. One month after operation, the right pupil was smaller than the pupil on the left side, that on which operation had not been performed. The arteries and veins of the right retina were larger than those of the left. Following cocainization, both pupils became dilated and were of equal size. Fifteen days after removal of the left lower cervical and first and second thoracic ganglia, the left pupil was smaller than the right and dilatation was not induced with cocaine, whereas in the right eye, dilatation occurred. The left palpebral fissure was narrower than the right. These observations indicate that the phenomenon had disappeared from the right eye but was present in complete form in the left eye. Fifty-seven days after the second operation, that on the left side, dilatation was obtained in both eyes following cocainization. At this time, Horner's syndrome was no longer complete in the left eye and was entirely absent in the right eye. In case 16, one of Raynaud's disease, in which bilateral excision of the lower and middle cervical ganglia was performed on June 10, 1926, operation was followed by bilateral partial ptosis and contracted pupils; these effects have persisted. Examination on Nov. 8, 1928, showed that both pupils were contracted and equal and that change was not effected by cocainization. Moderate and equal degrees of ptosis had persisted in both eyes. In case 13, the patient underwent bilateral removal of the lower cervical and first and second thoracic ganglia on Nov. 23, 1928. Eighteen days later both pupils were contracted. Dilatation was not obtained with cocainization. A complete Horner's syndrome was present. In case 36, that of a young man with scleroderma involving both hands and forearms, the left inferior cervical and first and second thoracic ganglia were resected on Dec. 11, 1928. Immediately after operation, the left

53. Jaboulay, M., and Ionescu, quoted by Diez (footnote 17).

54. Leriche, R., and Fontaine, R.: De quelques faits physiologiques nouveaux touchant les fibres oculo-pupillaires du sympathique cervical, Presse méd. **2**:1313, 1926.

pupil was contracted. A noticeable degree of ptosis was present. On the following day, the small vessels in the sclerotics and conjunctiva were dilated to a degree to simulate mild conjunctivitis. With cocainization, the left pupil was somewhat dilatated, indicating an incomplete Horner's syndrome. The vessels in the left retina were definitely dilated as compared with those on the side on which operation was not performed. Following resection of the right first and second thoracic ganglia, there was a transitory Horner's syndrome of the right eye which practically disappeared in ten days.

Comment.—Our observations on the ocular changes following cervical and dorsal ganglionectomy indicate: 1. Incomplete or temporary Horner's syndrome occurs after resection of the first and second thoracic ganglia; variations are noted in the right and left sides with the same operative procedure. 2. A more complete Horner's syndrome occurs after the operation if the inferior cervical portion of the cervicodorsal ganglion is also removed; a similar result was noted following resection of the middle and lower cervical ganglia and the effect in this case persisted for a period of thirty months. 3. Dilatation of the arteries and veins occurs constantly after both cervical and dorsal ganglionectomy. 4. Dilatation of the vessels of the sclerotics and conjunctiva occurred in the eye on the side on which operation was performed in one patient, and disappeared within five days. 5. Increased surface temperature of the face on the side on which operation was performed occurs with the ocular phenomena.

CUTANEOUS HYPERESTHESIA

Diez noted in his cases that after resection of the cervical sympathetic cord, cutaneous hyperesthesia of the skin appeared on the neck and usually disappeared in a month. After resection of the lumbosacral sympathetic chain, tenderness of the sciatic nerve was constant. In the thirty-six cases in our group in which the lumbar ganglia were removed, there were only two in which sciatic tenderness was present. It occurred in a mild degree and passed off within about ten days after operation. Hyperesthesia was not complained of or elicited on general examination in any case.

Following thoracic ganglionectomy, cutaneous hyperesthesia was noted in some degree in every case. In two cases this was fairly intense, and pain could be elicited after mild stroking of the skin of the arms. The hyperesthetic zone included the arms, neck and anterior and posterior surfaces of the chest to a level about 7.5 cm. below the clavicles. The area in the region of the wound exhibited the most marked hyperesthesia. Pain in the back, in the region of the wound, with disclosure on neurologic examination of irregular areas of anesthesia, was

constant. Soreness of the muscles, nerve trunks, and large arteries of the arm was brought out by mild palpation. Neurologic changes other than those mentioned accompanying this symptom were not present. The onset and duration of the hyperesthesia were variable, usually diminishing in from ten days to two weeks and completely disappearing at the end of four or five weeks. The individual sensitivity of the patient was undoubtedly a factor in the subjective severity of this complaint. It seems probable that the trauma of the first and second thoracic nerves during operation was the major factor in the causation of the pain. In the last three patients operated on, greater care was used in preventing trauma to these nerves; in these, the pain and hyperesthesia were minimal.

ATROPHY OF MUSCLE

Diez likewise called attention to atrophy of the pectoral, deltoid, trapezius, supraspinous and infraspinous muscles following resection of the middle, inferior cervical and first thoracic ganglia and trunk. Atrophy becomes recognizable in from one to three months. Atrophy of muscles was not noted after lumbosacral ganglionectomy.

We have not observed atrophy of muscles following lumbar ganglionectomy, at least not during the period of postoperative observation. In one case of Raynaud's disease studied for a period of three years after lumbar operation, atrophy of the muscles of the leg was not present. Following thoracic ganglionectomy, atrophy of the muscles of the shoulder was noted. There was considerable difference in the degree of atrophy present; in only one case was it striking, namely, in a case of scleroderma in which the trapezius muscle showed well defined atrophy four weeks after resection of dorsal ganglia.

SUMMARY

Physiologic studies carried out in thirty-six cases before and after lumbar ganglionectomy demonstrated certain changes after operation. Marked vasodilatation of the arteries of the feet and lower part of the legs, as measured by thermometric methods, persisted for periods as long as three years. Abolition of reflex sweating of the feet and lower part of the legs approximately to the level of the knees was a constant observation. Loss of pilomotor reaction occurred in approximately the same areas as did reflex sweating.

Following excision of the first and second thoracic ganglia the following conditions were observed: marked vasodilatation of the arteries of the hands, and mild vasodilatation of the arteries of the face, neck and upper part of the trunk, as measured by increases in the surface temperature. Loss of reflex sweating and pilomotor reaction

were in, roughly, the same region. The reaction of cardiac acceleration was preserved but possibly was diminished in degree. Horner's syndrome of variable intensity and persistence was a constant observation. The period of observation after dorsal ganglionectomy varied from one to six months, and vasodilatation did not diminish in that time.

The physiologic changes, indicative of a profound and apparently lasting effect on the vasomotor nerves, with vasodilatation, furnish adequate proof of the efficacy of these operative measures in certain forms of peripheral vascular disease.

DIENCEPHALIC AUTONOMIC EPILEPSY*

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Unlike the cerebrospinal nervous system, with its obvious and indispensable functions, the vegetative nervous system has been slow to come into its own. Only recently has its representation in the spinal cord and medulla oblongata been recognized, and still more recently its important representation in the midbrain and hypothalamus. The case I shall present would suggest that there are higher structures analogous to the cerebral motor cortex which are capable of producing, when irritated, paroxysmal motor discharges through the vegetative nervous system, similar to the focal discharges through the cerebrospinal system first described by Hughlings Jackson as epileptic.

REPORT OF CASE

History.—J. H., a woman, aged 41, entered the Presbyterian Hospital, New York, on Jan. 2, 1928, having been referred to me by Dr. Protzman of Englewood, N. J. She had had headaches ever since an accident to her head at the age of 5 years. The headaches were occipital and had been severe for at least twenty years. They occurred several times a week at first, but later they varied between several times a day and once a month. When the headache was severe enough she had a "spell" and she said that she became dizzy and might fall. Thirteen years ago, while sitting at the table, she suddenly cried out, "stiffened and fell under the table." She was unconscious for several hours and was thought to have had a convulsion which affected the arms, legs and neck.

Five years ago, there was a severe "attack of headache," and while "in coma" all her teeth were removed in the forlorn hope of reviving her. During this attack there were periodically recurring alterations in the condition, evidently identical with the seizures to be described. Nine days before admission, she had the most severe attack of all. During the six days of its duration, she again showed the recurring seizures.

The headaches had often come on suddenly following a movement, and sometimes were relieved just as suddenly as the result of some change of position, such as turning the head to the opposite side. She had always been clear mentally, and had shown a fortitude throughout that commanded the admiration of friends and family.

There was a history of an operation ten years previously for suspension of the uterus, and appendectomy. One year later, an exploratory laparotomy was done, with removal of part of the left ovary because of adhesions. At 5 years of age, the patient fell backward from a seven-foot wall, landing on her back and striking the back of her head on the concrete walk. She was unconscious for two hours.

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* From the Surgical Service, Columbia University, and the Laboratory of Neurocytology, Presbyterian Hospital, New York.

* Read at the Ninth Annual Meeting of the Association for Research in Nervous and Mental Disease, New York, December, 1928.

It is understood that blood came from her nose and ears. After she regained consciousness, she was up and about.

She had worn glasses for reading, but had no visual difficulty; there had been no diplopia. For the past eight years she had had gradual loss of hearing, the right ear being worse than the left. There had been no obstruction of the nose, and she had had no colds. The throat had been normal. There had been no cardiac or respiratory disorders. She had had a considerable amount of abdominal distention, and was often constipated. Nocturia, two or three times nightly, had been present. Menstruation had been regular until recently. The patient had two normal children, and had had no miscarriages. She had always been thin, but had gained a little weight recently. Her disposition had always been excellent.

The patient had two brothers who were deaf. There was nothing else of importance in the family history.

Physical Examination.—The important observations were as follows:

Cranial Nerves: First: Examination revealed complete absence of smell in both nostrils.

Second: The optic disk margins were blurred, especially on the nasal sides, and there was early papilledema. The retinal veins were fuller than normal. The visual fields were complete, and there was no enlargement of the blind spot.

Third, fourth, and sixth: The pupils were equal, but there was some irregularity of the left pupil.

Fifth: The corneal reflexes were present, but sluggish.

Seventh: Hearing was diminished in both ears; bone conduction was louder than air conduction.

Reflexes: The deep reflexes were present throughout and equal on the two sides. They were all unusually active, particularly in the lower extremities. The superficial reflexes were always found to be normal except that on two occasions examination showed that the left upper abdominal reflex was absent, while the left lower and the right abdominal reflexes were present.

There was a slight degree of exophthalmos. The fingers showed tremor when extended, and the feet were somewhat tremulous.

Special Examinations.—Roentgenography of the Skull, Jan. 10, 1928: The report of Dr. Ross Golden was as follows: "Stereoscopic films of the skull in the right lateral position show the floor of the sella to be intact, although apparently thin and not depressed into the sphenoidal sinus. The dorsum sellae is somewhat thin. The posterior clinoids cannot be seen. Films of the skull in the Grainger position show fairly well the greater part of the so-called Grainger line, which is the floor of the sella. It is not eroded, though thin. This evidence is very much against the presence of a pituitary tumor. This suggests rather that the erosion of the posterior clinoids is the result of pressure from above and probably behind."

Examination of the blood showed 3,680,000 red cells; otherwise the blood was normal. A Wassermann test of the blood and spinal fluid was negative. The temperature varied from 98.6 F. in the afternoon to a 100 F. in the morning. The pulse rate on an average was rather fast, from 80 to 100. The respiration rate was 20.

Course.—Ventriculography: A ventriculogram was done under local anesthesia; air was introduced directly into the ventricle through one occipital lobe. The fluid was clear; the pressure was 250 mm. of water after about 10 cc. had been lost. Respiratory and cardiac oscillations in the fluid were marked. Ninety cubic centimeters of fluid was replaced with air without discomfort.

The ventriculograms showed enormous symmetrical dilatation of the lateral ventricles (fig. 1). In this figure also the convolutional atrophy of the skull due to long continued intracranial pressure is evident. In a lateral plate taken with the brow down, the posterior horns were shown (fig. 2), but there was also a third shadow [1] situated above the tentorium over the roof of the midbrain and between the occipital lobes of the cerebral hemispheres. The third ventricle was not shown in any of the plates and the conclusion from the plates alone was block in the third ventricle.

Headaches: On the day following admission, the patient stated that she was lying in bed with her head on the left side; she was straining to void when

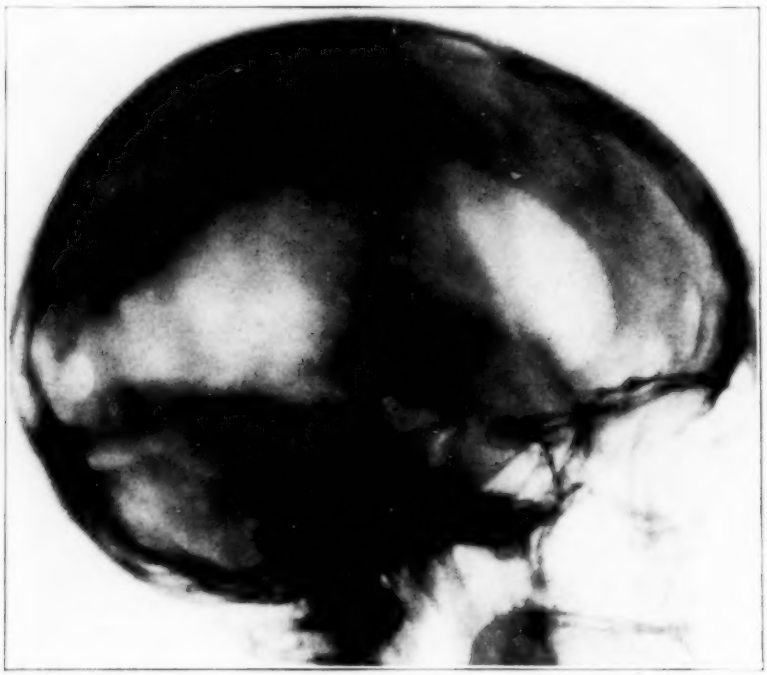

Fig. 1.—Enlargement of lateral ventricle shown by ventriculography. Note the convolutional atrophy.

suddenly she felt a sharp pain which extended from the lower occipital region along the midline. She "wriggled" her head about to the other side to change the position in the hope of stopping the pain. She felt stifled and had profuse

1. The location of this cavity was verified by autopsy; it was shown to communicate with the lateral ventricles of both sides through a defect in the tela choroidea below the splenium of the corpus callosum. I have seen such a cavity associated with internal hydrocephalus in four other cases, one of them verified by autopsy.

So far as I am aware the recurrence of this collection of fluid has not been previously pointed out. Although the cavity is surrounded by arachnoidea, it is outside the subarachnoid space.

diaphoresis. All symptoms disappeared after voiding. Her hands trembled for a time following the attack. Except for this there were only occasional headaches during the first days in the hospital, and these were not increased by ventriculography.

A diagnosis of tumor in the third ventricle was made, but operation was delayed for a few days.

Beginning on January 11, the fifth day after the injection of air, she had a headache and vomited. After twenty-four hours, it developed into a "headache attack" which, according to the patient and to her husband, was identical with the attacks from which she had suffered periodically for years.

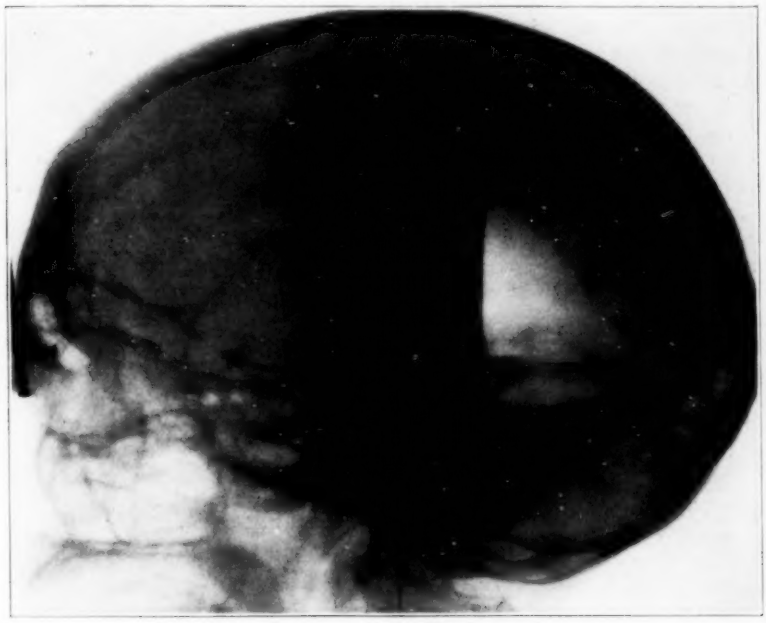

Fig. 2.—Roentgenogram taken with the brow down. Note air in the posterior horns of both lateral ventricles, also in the midline cavity over the roof of the midbrain. The posterior clinoids have been absorbed.

On January 12, while suffering from the headache, she was given an enema. During the procedure the nurse noted the following: "She suddenly became flushed and had profuse diaphoresis. Pulse 126, rather irregular but of good quality." Following this attack I saw her and the pulse was irregular and weak. Her face was pale. She was not perspiring. Hoping to dislodge the tumor from an unfavorable position I moved the head, turning the face down. She then suddenly flushed down to her breasts. There was no flushing of the feet, but she perspired profusely and suddenly over the whole body. The pupils were small and equal and reacted to light both directly and consensually. The deep and superficial reflexes were about as before the attack, the abdominal reflexes being present, and the plantar responses indeterminate. There was transient ankle clonus.

From that time on the headache was apparently continuous. She lay most of the time without moving, in obvious pain. She would answer questions briefly but clearly. At recurring intervals she had an attack in which the same phenomena reappeared regularly. The attack was explosive and heralded by prodromal symptoms and the phenomena followed a fixed order just as may happen in a series of epileptic convulsions or status epilepticus. The amazing feature of each seizure was that the succeeding motor phenomena were confined to the structures controlled by the vegetative nervous system.

Description of Attacks.—A typical attack may be described as follows: The patient stirred and asked for cracked ice. Then her face and arms flushed a deep red. She lay quietly and respirations became very slow. Tears rolled from both eyes and fell on the pillow. She broke into a profuse diaphoresis over the entire body. Saliva ran out of the corner of the mouth. The eyes were open; the pupils were large and the eyes protruded.[2]

The pulse was strong and rapid. Gradually the flushing faded, the pulse became weak and slow. The patient then hiccuped from three to five times, and this was followed shortly by transient shivering. The respirations became of the Cheyne-Stokes type. She could be roused to questions throughout the attack, but she would answer briefly.

Late on the night of January 12, the attacks became more severe. She was unconscious during them. The duration of each attack was from five to twelve minutes, and several were followed by shivering of five minutes' duration. The temperature fell to 97 F. During one attack she was incontinent. Occasionally, there was a shivering or a hiccuping without an attack, and occasionally tears and diaphoresis did not follow the flushing. During one of the more severe attacks the respirations became much slowed and stopped for a brief period. She was seen by Dr. Cone, who punctured the lateral ventricle through one of the trephine openings made for the ventriculography. There was a sudden escape of air and fluid under such high pressure that a bit of cerebral tissue was blown through the brain needle onto his cravat. Following the puncture she regained consciousness.

A few hours later, in an unusually severe attack, respirations practically failed and he punctured the other ventricle, again removing air and fluid under much increased pressure. At the time of this puncture she seemed unconscious, but immediately following it she said she felt better. She shivered violently then for about five minutes.

After these attacks had continued at recurring intervals for about twelve hours, it was recognized that although the motor discharges were confined to the autonomic nervous system, the association of the phenomena with a tumor of the third ventricle made it evident that the condition was analogous to status epilepticus. Consequently, sodium bromide was administered and was followed by steady improvement in the patient's condition. Either post hoc or propter hoc, the attacks became much less severe and less frequent, and the patient began to talk and eat. She had been able to eat a little, however, even between severe attacks and did not vomit during them. For a time a few hiccups followed whenever she drank anything. She had been unable to void to command while the headache lasted, and she could now do so only on getting out of bed.

On January 16, the condition seemed satisfactory, although she was having trouble as usual with constipation and inability to void. It was therefore determined to proceed with a craniotomy and removal of the tumor of the third ven-

2. Protrusion of the eyes was not invariably present.

tricle through the lateral ventricle on the following day. While blood was being taken for examination that evening, she suddenly flushed and seemed to have air hunger, but none of the other characteristics of an attack. She had a few attacks during the night.

At 5 a. m., just four hours before the scheduled operation, she had a severe attack. Respirations stopped for about five minutes. Artificial respiration brought her back and she seemed to be rallying when there was another sudden change, perhaps a second attack, and she died at 5:30 a. m. The notes of the patient's nurse are remarkably vivid and accurate.[3] They are therefore added here without alteration.

Jan. 13, 1928, 7:20 a. m.: Attack characterized by previous symptoms. Cheyne-Stokes breathing preceded attack for 4 min. approximately. Flushed face. Profuse diaphoresis and slow, labored breathing, lasting 10 min. Unconscious for 15 min. Cheyne-Stokes breathing followed attack and lasted for 8 min. Patient invariably asks for ice just before attack. Patient comfortable. No headache. Cold only complaint.

8:15 a. m.: Attack lasting 10 min. Face flushed. Profuse diaphoresis. Breathing rapid at onset (30) becoming Cheyne-Stokes in character. Slowest rate 6. Pulse 100 and full at onset becoming weaker and slower. Eyes fixed at onset. Attack followed by severe shaking chill lasting 5 min. Temperature 100. Salivation present during attack. Tears came from both eyes slowly.

9:00 a. m.: Attack. Much like last one. Tears and salivation both present. Flush and diaphoresis. Duration 12 min. Unconscious.

9:35 a. m.: Attack lasting 5 min. Tears, slight salivation. Flush, diaphoresis, unconscious. Eyes open, prominent and fixed at onset. Followed by two attacks of shivering about 4 min. after end of attack. Incontinent.

10:07 a. m.: Attack lasting 4 min. Unconscious for approximately 10 min. Tears. No salivation apparent. Pulse weaker. Resp. 4. Flush present but not at onset. Shivering at 7 min. intervals for approximately 4 sec., three times. Patient has been conscious and quieter. Breathing more easily and regularly than at any time since turned on back. Now on right side and apparently comfortable.

11:02 a. m.: Attack lasting 4 min. approximately. Slight. 1st, changed respirations, labored 6-4. 2nd, flush, not very pronounced. 3rd, slight salivation. Resp. Cheyne-Stokes but easier at 11:05. Tears at 11:05. No apparent loss of consciousness. Followed by 3 sec. attack of goose-flesh, shivering and hiccups. Says she wants to sleep. Slept from 11:20 to 12:15 quietly.

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3. The accurate records of Miss Hilda Minshall have contributed largely to the value of these observations and indicate the high level of nursing efficiency in the Presbyterian Hospital Training School.

12:15 p. m.: Attack lasting 9 min. 1st., asked for ice; 2nd, face became flushed. Resp. labored and irregular (4-5 a min.); 3rd, diaphoresis; 4th, tears and salivation. Unconscious from onset till 12:25.

1:25 p. m.: Attack lasting 12 min. 1st, deep sighing respirations. 2nd, flush. 3rd, loss of consciousness. No salivation or tears. Conscious at 1:37 but respirations irregular till 1:45. Attack of hiccups at 1:45. Lasted only about 30 sec. No shivering.

2:05 p. m.: Short attack. 1st, restless, moving of hands and feet. 2nd, flushing of face. 3rd, change in respirations. Tears, salivation and loss of consciousness. Regained consciousness before flush disappeared. Patient dozes most of the time between attacks but is perfectly clear mentally when addressed and is very co-operative. Says her head aches "off and on."

3:30 p. m.: Attack lasting about 5 min. 1st, restlessness. 2nd, convulsive breathing. 3rd, flushed face, tears and salivation. This came on almost immediately after moving patient from one side to the other. Pulse did not go to pieces quite so much as usual. Hiccuped 4 times after attack. After attack, but while she still had Cheyne-Stokes breathing, it was noticed that goose-flesh appeared on her forearms while breathing, and disappeared in each interval between breathing spells.

5:02 p. m.: 1st, restlessness. 2nd, flush. 3rd, convulsive respirations. 4th, diaphoresis. No tears or salivation. Duration 6 min. Hiccuped 3 times 5 min. after. Pulse not as good quality since 4:00 p. m. Hiccuped 5 times at 6:15 p. m.

6:40 p. m.: 1st, restlessness. 2nd, flush, convulsive breathing. 3rd, loss of consciousness. 4th, diaphoresis. Patient was conscious during first few seconds of attack. Tears and salivation both present. Hiccuped 3 times and moved legs convulsively after attack but did not shiver then. Duration 5 min. Pulse 96. Resp. 6. Just before attack patient had taken 2 ozs. of oatmeal gruel and said that it was good. Shivered 5 min. after attack was over, twice for 30 sec. with a 60 sec. interval. Hiccuped twice at 6:55 p. m. Quiet and dozing.

7:30 p. m.: Hiccuped 4 times.
Face flushed, slight diaphoresis on face 30 sec. Conscious and says she is comfortable. Respirations of slight Cheyne-Stokes character continue.

8:15 p. m.: Hiccuped three times. Slept for ½ hour.

10:10 p. m.: Hiccuped four times.

10:15 p. m.: Face and arms flushed, shivering. Slight tremor over body. Convulsive respirations for 60 sec., salivation. Pulse 96. Resp. 8. Diaphoresis. Eyes fixed and staring with apparent loss of consciousness for 60

sec. of convulsive respirations. Mucus in throat since attack. Asks to have the light put out and not to be disturbed as she wants to sleep. Slept from 10:30-11:00 p. m. Resp. 16, deep and regular. Pulse at 11:00 p. m. somewhat thready—104. Hiccuped six times at 11:00 p. m. and 4 times at 11:20 p. m. Dozing again. Conscious when roused. Respirations irregular—Cheyne-Stokes. No headache—no pain. Wonders what gives her hiccups. Does not like being disturbed every little while. Dozing and quiet from midnight until about 5 a. m.

Restless and wakeful between 5 and 6 a. m. No attacks after 10:15 p. m. Conscious when roused. No headache. Hiccuping at intervals, not continuous.

1:00 a. m.—6 times.
1:45 —8 times.
2:20 —6 times.
4:00 —8 times.
5:00 —3 times.
5:15 —6 times.
5:45 —4 times.

Resting and sleeping between 6 and 7 a. m. Respirations through night varied and irregular for the greater part of the night resembling Cheyne-Stokes at times.

January 14: Frequently 6 breaths for ¼ min.; 0 for 2nd ¼ min.; 6 for 3rd ¼ min.; 0 for 4th ¼ min. Varying in quality—sighing or puffing expiration. Respirations quiet and regular between 6 and 7 a. m. No diaphoresis except slight in attack at 7:30 and 10:00 p. m. Has not voided through the night. Sleeping very quietly with regular respirations from 7:15 to 8:40. Pulse fair quality, regular rate about 90-80.

Hiccuped—8:40 a. m.—2 times.
8:48 —4 times.
8:57 —5 times.
9:17 —4 times.
9:45 —4 times.

Is thirsty and sleepy, wants to be let alone. Complains of pain in bladder. Lower abdomen quite distended. Unable to void naturally even though sitting up. Asked to be catheterized. Poultice to lower abdomen but no effect. Tried again to void sitting on edge of bed but without success.

Hiccuped—10:25 a. m.—2 times.
10:45 —2 times.
10:50 —4 times.
10:55 —2 times.
11:00 —3 times.
11:10 —4 times.

Always hiccups 3-4 times after drinking. Appetite very poor. Voided naturally sitting on commode

525 cc. Somewhat bothered by gas. Bowels moved (liquid small amount) at 2 p. m. Hiccuped ten times after drinking at 2:15 p. m. Mentally clearer than at any time. Says she "feels much better."

2:00 p. m.: Sleeping quietly and breathing naturally for long periods. Shivered for 30 seconds but no other change.

Hiccuped—1:00 p. m.—3 times.
2:05 —4 times.
3:10 —5 times.
3:55 —2 times.
4:15 —9 times.
4:55 —2 times.
5:40 —3 times.
6:15 —5 times.

Awake, quiet and comfortable during evening. Pulse 90, respiration 16, regular.

January 15: 9:00 a. m. Hiccuped twice after drinking at 9 a. m. Took a few teaspoonfuls of coffee and half a grape fruit for breakfast. A few eructations of gas this a. m. No discomfort, no headache. Comfortable, taking fluids well.

Hiccuped—10:25 a. m.—3 times.
11:20 —once.
12:00 —twice.
2:00 —3 times.
4:15 —twice.

5:00 p. m. Quiet comfortable day. No attacks. No pain. Bright and cheerful. Appetite slightly improved, but still very poor. Takes fluids well, however.

January 16: 7:30 a. m. Comfortable this a. m. except for feeling of "pressure" in lower back of head. This has increased in severity until very troublesome by 1 p. m. No relief from medications. Unable to void this a. m.

10:00 p. m. Slight attack. Flush on face—four sighing respirations. Eyes fixed for an instant. Slight diaphoresis on face. Conscious and says she is comfortable. Pulse, 72; resp., 12; temp., 97.4. Extremities warm. Quiet and sleeping again. Respirations regular.

11:00 p. m. Complained of "head aching quite badly." Took bromide 1 Gm. and drank 100 cc. water.

January 17: 1:00 a. m. Attack lasting 5 min. Complained of headache—restlessness. Flush over face and arms. Convulsive respirations and heavy sighing. Eyes fixed and staring widely, tears and salivation. Saliva slightly frothy. Loss of consciousness through the attack. Respirations 7 and later 12—irregular. One long sighing and one short, alternating. Conscious after attack but rather sluggish. Asked for ice but took fluid grudgingly—said she wanted to sleep. Slept quietly—respirations becoming regular. Hiccuped once.

2:30 a. m. Attack 3 min. Said she felt warm. Face and arms flushed—asked to be sponged off and for a piece of ice. Convulsive respirations—5 per min.—regular—eyes staring, tears, salivation. Loss of consciousness. Diaphoresis over face and arms. Respirations somewhat stertorous but regular and rising to 7 and 9.

2:45 a. m. Attack 3 min. Face and arms flushed. Convulsive respirations 5, regular, stertorous, eyes staring. Tears, salivation, unconsciousness through attack. Saliva frothy. Respirations irregular, rate 5-10. Patient holding breath for 30 sec. and 5 or 6 for the second 30 sec. Alternating with regular respirations at 10 or 12 for each 60 sec. Conscious but sluggish. Said her head felt better. Took a little broth and cracked ice. Respirations continued irregular. After pause of 15 to 20 sec. respiration is resumed at rate of 10-12 per min. Diaphoresis over entire body.

3:00 a. m. Sodium bromide given. Cessation of respiration for about 2 min. Artificial respiration resorted to with success. Started breathing again and spoke. Occurrence of attack followed by stertorous breathing and cyanosis of face—eyes fixed and staring, slight froth in mouth. Pulmotor used without effect and breathing ceased. Pulse regular and fair through the night (becoming thready during attacks) and ceased at 5:30 a. m. after respirations stopped.

Report of Autopsy.—With the permission of Dr. von Glahn of the Pathology Department I was able to carry out this examination personally three hours after death.

Gross Observations: The hair was normal in distribution. Two healed incisions were present over the occipital pole. The skull was normal in size, shape and thickness. There was some convolutional marking on its under surface.

The dura mater was thinned. It seemed to be under considerable tension. There were rather marked small herniations in the temporal fossa such as are often associated with increased intracranial pressure. There were no particular adhesions to the arachnoid. The sinuses appeared normal.

The pia-arachnoid was normal in color. There were no opacities and there was no evidence of exudation. The cerebrospinal fluid spaces at the base of the brain were full and not collapsed; this was true of the peribulbar and interpeduncular spaces. The cisterna magna was obliterated by the marked herniation of the cerebellum. The intergyral fissures were practically obliterated, owing to convolutional flattening.

There is marked congestion of the brain itself. However, this was noted only of the brain and the cerebellum, the pons being pale as will be described.

The brain weighed 1,500 Gm. The organ was rather red in appearance and of normal consistency. The hemispheres showed great convolutional flattening.

The medulla and pons were strikingly white and only the larger pial vessels were here visible. In contrast with this, the cerebrum and cerebellum were unusually red and suffused, many small pial vessels being visible (fig. 3).

The lateral ventricles were greatly dilated, but the fourth ventricle was of normal size. The third ventricle was not dilated, but in its anterosuperior portion, protruding into the foramens of Monro on each side and pushing the overlying

fornix upward, was to be seen a round, pearly white tumor (fig. 4). It was covered with a loose capsule formed by a sheet of tissue which was continuous with the choroid plexus as it appeared in the foramen of Monro. When this capsule was opened the tumor fell out, round like a marble and with no attachment. Although the situation of the neoplasm was within the third ventricle, it pushed the pillars of the fornix upward and thus pressed on the mesial anterior and superior aspect of the thalamus of each side.

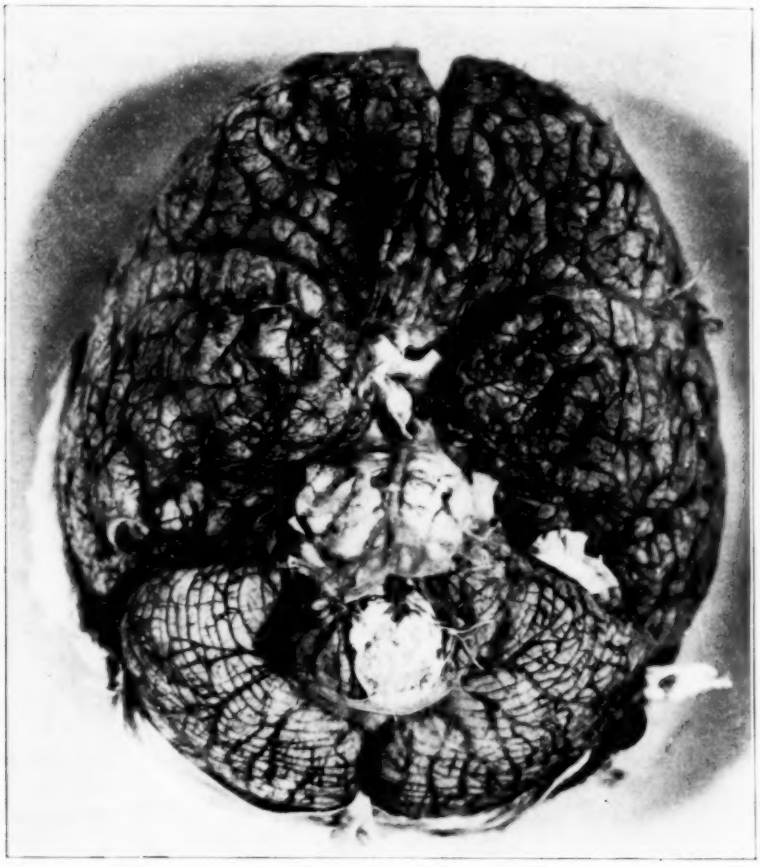

Fig. 3.—Photograph taken immediately after the necropsy and before fixation. Pallor of the brain stem is in striking contrast to the unusual suffusion of the rest of the brain.

The posterior end of the corpus callosum was raised, and a defect through it caused a communication to exist between the lateral ventricle of each side and a cystic cavity bounded above by the cerebral hemispheres, posteriorly by the cerebellum and below by the roof of the midbrain.

The retina showed swelling of the nerve head with exudation of lymph, most marked about the disk, but also seen along retinal vessels (fig. 5).

Microscopic Examination: Examination of the thalamus showed that the nerve cells and neurofibrils were normal throughout. Neuroglial astrocytes and oligodendroglia were also normally preserved, and showed no abnormal reactions. There was perhaps some increase in the number of oligodendroglia cells of the white tracts beyond the normal number. In the brain stem the nerve cells seemed

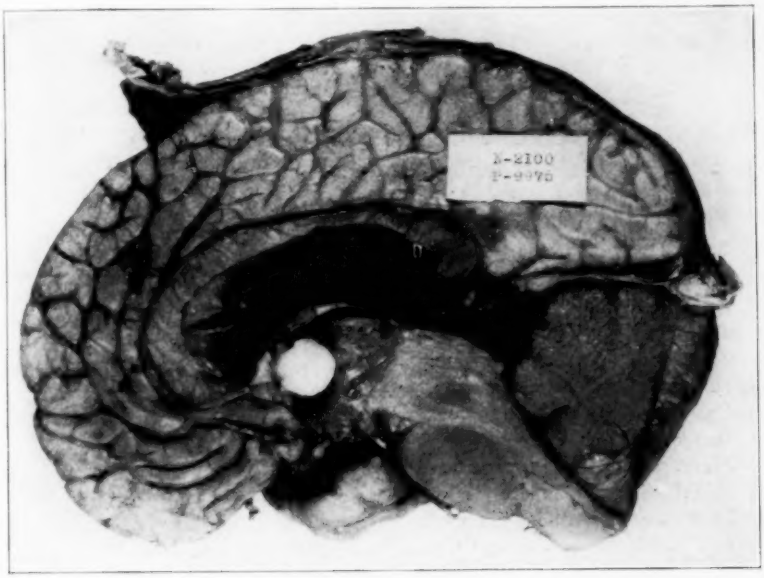

Fig. 4.—Longitudinal section of the brain, after fixation, showing a cavity over the midbrain connecting with the lateral ventricle, and a "pearly tumor" presenting in the foramen of Monro and covered by the arching band of fornix.

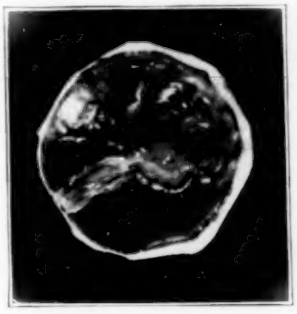

Fig. 5.—Excised retina showing early edema of the nerve head and patches of exudate.

to be normal, as shown with toluidin blue. The blood vessels here contained no corpuscles.

In the area beneath the ependyma, where the tumor impinged and where grossly edema and cavitation were seen, there was fading out of cell structure. The neurofibrils did not stain with silver and the astrocytes were not impregnated by

gold chloride. The tissues were separated by fluid. There was, however, no evidence of reaction—no gliosis and no fat-laden cells—but there seemed to be some increase in the number of local blood vessels.

Finally, the areas just mentioned were evidently produced by acute edema, being the immediate effect of the pressure preceding, or immediately following, death.

The tumor was made up of much structureless material, some of which suggested epithelial débris. It evidently was a "pearly tumor," or cholesteatoma.

COMMENT

The following outline will serve to give the sequence of phenomena as they appeared in succeeding attacks:

1. Prodromal[4] (restlessness; request for ice in mouth)
2. Sudden vasodilatation of skin in area supplied by cervical sympathetic
   Sudden rise in blood pressure
3. Lacrimation
   Diaphoresis
   Salivation
   Dilatation (or contraction) of the pupils
   Protrusion of the eyes (not invariable)
   Increase of rate and pressure of pulse
   Marked retardation of respiratory rate
   Elicitability of pilomotor reflex
   Loss of consciousness (rare)
4. Disappearance of superficial blush and fall of blood pressure slowing and weakening of pulse
5. Hiccuping (from 3 to 5 in number)
6. Transient shivering
7. Cheyne-Stokes respiration (apparently the result of but not a part of the attacks)

Blood Pressure.—On one occasion the patient's systolic blood pressure was measured in the brachial artery at 110 mm. of mercury. Just as the determination was finished and before the cuff was removed, the nurse predicted an attack because of the patient's restlessness. Immediately the pressure was measured again. It had risen to 190. Deep red flushing appeared. The pressure when retaken was 200 systolic and 100 diastolic. The next determination was 210. The pressure then rapidly fell to 160, 140, and 122 systolic and 75 diastolic. About five minutes after the close of this attack, the pressure was 94 systolic and 68 diastolic. This was a typical attack and the sphygmomanometric readings would doubtless have been similar had they been taken during other attacks.

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4. The prodromal symptoms were not recognized by the patient herself, but her nurse could readily predict an attack thereby. The restlessness was only slight, but it was noticeable as the patient usually lay quiet between attacks.

Pilomotor Disturbance.—On several occasions the nurse recorded in her notes that during the period of Cheyne-Stokes respiration that followed an attack, "goose flesh" could be seen to appear over the patient's shoulder with each recurring increase in the respiratory rate. During the succeeding periods of apnea, the "goose flesh" disappeared. This was not always the case. But it was observed that, during the time when the patient was flushed in an attack, a pilomotor reflex could be very readily elicited by stroking the skin of the arms or trunk with a pin. At other times, it was found impossible to elicit the reflex.

Micturition.—There was incontinence of urine in one severe attack only. On the other hand, from the onset of each series of attacks until they were over, the patient was unable to void and had to be catheterized. This had also been found necessary in her previous attacks at home.

Body and Extremities.—There was never any movement of the body to suggest convulsions of the extremities or trunk. The patient lay quietly throughout the attacks, and she usually answered questions in monosyllables.

Temperature Control.—During the most severe series of attacks, the temperature fell well below normal. Neither the transient shivering that followed each seizure nor the occasional attacks of shivering of longer duration seemed to cause a noticeable rise of temperature.

Diagnosis.—It seems obvious, therefore, that the recurring seizures from which the patient suffered were made up of discharges from the centers which control the vegetative nervous system. Such centers controlling the blood vessels, the heart, sweating, temperature, etc., have been placed tentatively by workers in the hypothalamus about the third ventricle.

The acute softening found in the thalamus of one side, apparently due to the pressure from the tumor lay anterior to and above these nuclei. This localized edema was evidently of only a few hours' standing. Four horizontal cuts were made through the basal ganglia of one side. The area of edema extended down as far as the anterior commissure but no farther (fig. 6, I-IV). This area of edema did not necessarily signify the maximum area of pressure, but for the sake of completeness in the report, its description is given. There was also a small cavity farther posterior as shown in block *I* of fig. 6. This also was not of over a few hours' standing as proved by microscopy.

The pressure of the tumor, held loosely as it was in its capsule, was brought to bear on the thalamus symmetrically on the two sides. This pressure came against the dorsal nucleus (anterior) of the thalamus, and the tissue below and anterior to this. The fornices were stretched over the tumor. This may account for the complete loss of smell. There must have been pressure on certain nerve tracts as well, i.e., the mamillothalamic fasciculus (Vic d'Azyer), anterior commissure and anterior peduncles of the thalamus.

The tumor contact and pressure was clearly above and anterior to the nuclei of the hypothalamus (fig. 7) which have been assigned as head ganglia for the vegetative nervous system, being well above the groove which separates thalamus from hypothalamus.

It seems to be an unescapable fact that the autonomic convulsions were set off by the irritating presence of this movable tumor, intensified by the cerebrospinal fluid pressure on the tumor when it had become

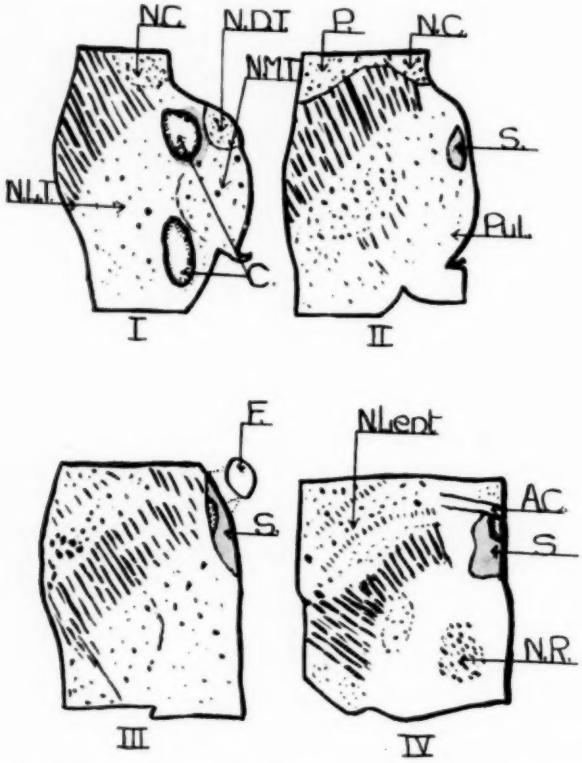

Fig. 6.—Horizontal blocks cut through the basal ganglia of the left hemisphere, beginning at the top. *S.* indicates softening; *N.C.*, nucleus caudatus; *N.D.T.*, nucleus dorsalis thalami; *N.M.T.*, nucleus medialis thalami; *N.L.T.*, nucleus lateralis thalami; *C.*, cavity; *P.*, putamen; *Pul.*, pulvinar; *F.*, fornix; *N.Lent.*, nucleus lenticularis; *A.C.*, anterior commissure; *N.R.*, nucleus ruber.

wedged into the formamina of Monro, thus shutting off the flow of fluid from the lateral ventricles to the third ventricle. The history of discontinuous headache, which could be started and stopped by alterations of position of the head or body, indicates that the tumor acting as a ball valve was at times wedged in between the thalami and at others gave free passage to spinal fluid. This pressure may likewise cause obstruction

to the outflow of venous blood from the choroid plexuses, thus further increasing the ventricular pressure by augmenting the formation of fluid by the plexuses.

The evidence therefore points to mechanical irritation of some center or conduction path capable of setting into action the ganglia which exert control over vascular apparatus, sweat and tear glands, etc. One can only theorize in such a case as to what the identity of the involved structures above these centers may be.

It is in a sense a physiologic requirement that the thalamus, the structure where painful stimuli rise into consciousness, should have a close connection with the control of those vegetative functions which are almost invariably called into action as the result of severe pain or other strong emotions.

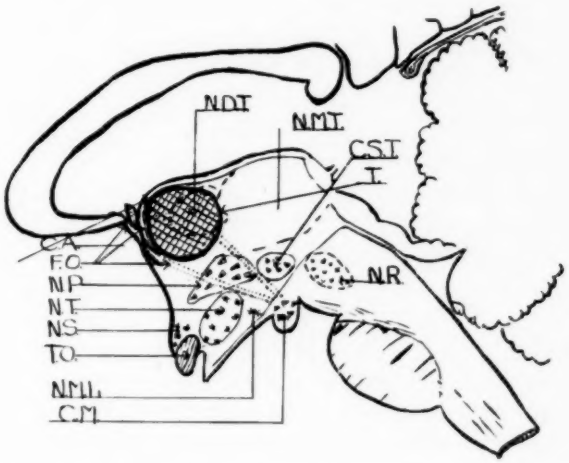

Fig. 7.—Site of tumor roughly indicated by cross hatching on a scheme of the paraventricular nuclei. *N.D.T.* indicates dorsal (or anterior) nucleus of thalamus; *N.M.T.*, nucleus medialis thalami; *T.*, situation of tumor; *F.O.*, fornix; *N.P.*, nucleus paraventricularis (Malone); *N.T.*, nucleus tuberis; *N.S.*, nucleus supraopticus; *T.O.*, tractus opticus; *N.M.L.*, nucleus mamilloinfundibularis (Malone); *C.M.*, corpus mamillare; *C.S.T.*, corpus subthalamicum (Luys 2); *C.A.*, commissure anterior.

There appears to be no direct downward path from the thalamus to the paraventricular gray nuclei, but Greving [5] pointed out in his excellent outline (1928) that there are fiber connections with these centers from the thalamus by way of the corpus striatum. From the thalamus to the corpus striatum runs the anterior peduncle of the thalamus. From the

5. Greving, R.: Die zentralen Anteile des vegetativen Nervensystems, Handb. d. mik. Anat. d. Mensch. **4**:917, 1928.

striate body impulses may pass through the ansa lenticularis viâ the globus pallidus to the corpus subthalamicum (Luys). Also there is probably a direct path, the striohypothalamic. Fibers from the striate body also evidently pass to the nuclei tuberis viâ the frontotuberal tract and to the nucleus supra-opticus viâ the frontosupra-optic tract.

There has been presented at this meeting what is in some ways the most convincing proof of direct diencephalic autonomic control, i.e., of metabolism within the heart and of epinephrine secretion (Beatty, Long and Brow). The acute stimulation experiments of Karplus and Kreidl show that electrical stimulation of the hypothalamus produces sweat secretion, and it has been suggested that lacrimation and salivation are also under direct nervous control from somewhere in the hypothalamus.

The phenomena which presented themselves in the convulsive seizures of this patient were obviously under direct nervous control, not only from the hypothalamus but from a somewhat higher placed neurologic mechanism.

The production of jacksonian epilepsy by an irritative focus in the cerebral cortex is analogous to the production of the autonomic epilepsy displayed by this patient. A comparison may therefore be suggested between the region bilaterally pressed on by the tumor in this case, and the corticomotor apparatus of the cerebral hemispheres. It indicates that in the thalamus and not the hypothalamus lies the highest representation of the vegetative nervous system.

CONCLUSION

A series of motor phenomena in the control of the vegetative nervous system have been described which are analogous to attacks of jacksonian epilepsy. The irritative source of the attacks was evidently an encapsulated tumor which periodically pressed on the thalamus of both sides, as described.

Autonomic epilepsy is a new conception in neurology. It is suggested as a result of the study of this case that the vegetative nervous system may have a representation as high as the anterior nucleus of the thalamus. No attempt, however, is made to isolate the involved centers.

THE NERVE SUPPLY OF THE CEREBRAL BLOOD VESSELS

A HISTOLOGIC STUDY *

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François-Franck [1] justly stated that the vascular innervation of the central nervous system may conveniently be studied on the blood vessels of the pia, for the latter "practically belong to the brain substance itself." It must also be conceded that the vasomotor nerves of the pia are derived from the cervical sympathetic nerve supply of the internal carotid and the vertebral arteries; the vertebral system innervates the blood vessels of the pons, medulla and cerebellum; the carotid system supplies the rest of the cerebral vessels. The pia receives additional—parasympathetic—nerves from the third, seventh, ninth and tenth, and also some fibers from the sixth, eleventh and twelfth cranial nerves. Some nerves have apparently nothing to do with the vascular innervation, for they end freely in the connective tissue. Some such fibers are most likely sensory.

METHODS OF STUDY

Ordinary dissecting methods of studying the vascular nerves can be applied only to the larger blood vessels, such as those of the carotid and the middle cerebral arteries. For smaller blood vessels, the refined, so-called "macro-microscopic" methods of Worobiew [2] and his pupils [3] are valuable, while the nerves of minute blood vessels (arterioles,

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* From the Pathologic Laboratories of the Research and Educational Hospitals of the University of Illinois and the State Psychopathic Institute.

1. François-Franck: Recherches sur les nerves vasculaires de la tête, Travaux du laboratoire de Marey, Paris, Masson & Cie., 1875, mémoire 8.

2. Worobiew, W.: Methodik der Untersuchungen von Nervenelementen des makro-u.-mikroskopischen Gebietes, Berlin, Oscar Rothacker, 1926.

3. Kondratjew, N. S.: Eine neue Methode der elektiven makroskopischen Färbung des Nervensystems, Ztschr. f. Anat. u. Entwcklngsgesch. **78**:669, 1926. Ljetnik, S.: Die Verteilung der Nervengeflechte in der Adventitia der Gefässe (Zur Frage der periarteriälen Sympathektomie), Anat. Anz. **59**:467, 1925.

venules and capillaries) can be studied only with special microscopic staining methods. Of these the most important are Ehrlich's intravitam methylene blue (methylthionine chloride, U. S. P.) method and its modifications, and the silver staining method of Schultze. The methylene blue method was used by me in the form of intracerebral injections of a few drops of 1 per cent solution of methylene blue. The pia-arachnoid, as well as the contents of the subarachnoid space, stained readily, but the nerve fibers remained unstained. I used this method

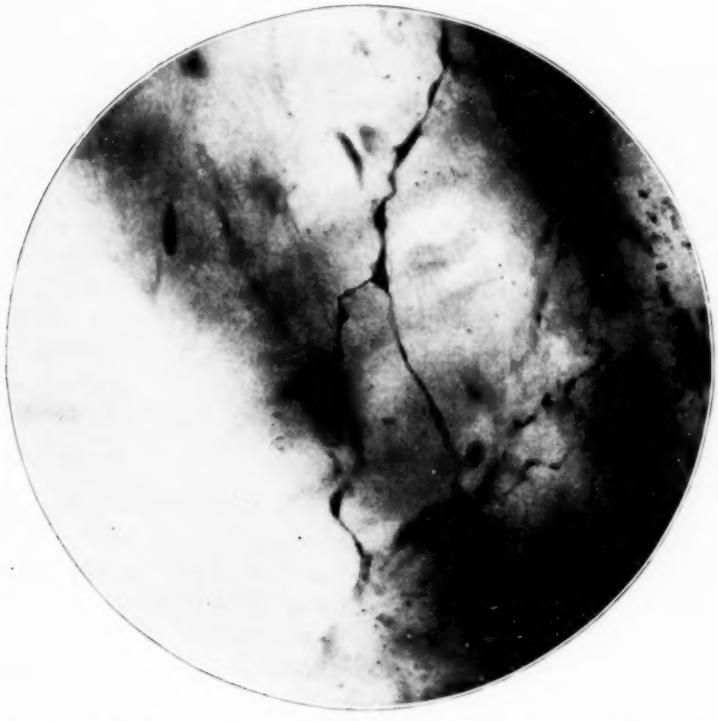

Fig. 1.—Dog's brain. The adventitia of a small artery (0.12 mm.) showing nonmedullated varicose nerve fibers. The varicosities are especially marked near or at the point of bifurcation. The left fiber also shows two Schwann cells, one of which (the lower) is adjacent to the varicosity. Other nerves can be seen to the right; those to the left are indistinct (out of focus). Schultze-Stöhr silver stain; × 640.

on a limited number of rabbits and discarded it in favor of the silver staining method of Schultze. It was used as follows:

The material is hardened in a diluted solution of formaldehyde U. S. P. (1:10); two days later, small pieces of pia or pial blood vessels are carefully dissected and placed in toto, for twenty-four hours, in a 20 per cent dilution of a normal (4 per cent) solution of sodium hydroxide (this is kept in stock); several

changes of distilled water for about from one to two hours; 10 per cent solution of silver nitrate, for from twelve to sixteen hours; reduction in a mixture of hydrochinone-formaldehyde. This mixture (hydrochinone, 2.5 Gm.; distilled water, 100 cc.; solution of formaldehyde, 5 cc.) is also kept as a stock solution and before being used should be diluted (1:80 or 1:120). I have used a 1:80 solution, that is, 1 drop of hydrochinone-formaldehyde in 79 drops of distilled water. Here the tissues stay about one second and are examined under the microscope for the presence of nerve fibers. As soon as such are noticed, the tissues are rinsed in distilled water (twice), passed through alcohol (95 per cent) and car-

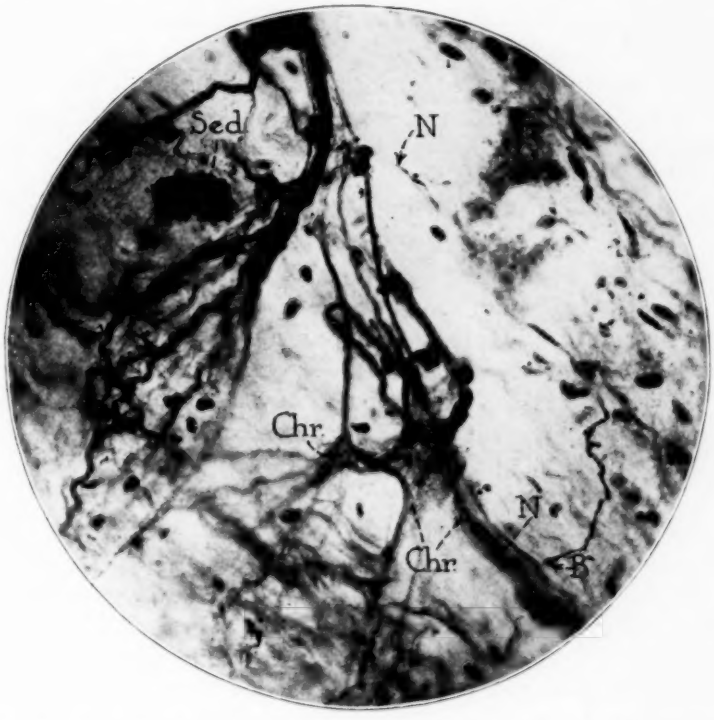

Fig. 2.—Dog's brain. The center of the picture is occupied chromatophore (*Chr.*) cells and their large processes, of which the right lower one contains several dark thin nerve fibers (*N*); to the right of this chromatophore process is a small winding nerve fiber ending, near the process, in a small bulb (*B*); Sed., sediments (size of the blood vessel, 0.4 mm.). Schultze-Stöhr method; × 320.

bolxylene, and mounted in Canada balsam. If the hydrochinone-formaldehyde solution becomes somewhat cloudy it should be changed.

The nerve fibers appear as black threads; the myelin, brownish, and the rest of the tissues, pale yellow or brown according to the length of time they have been kept in the hydrochinone-formaldehyde solution. If kept too long, all the tissues turn dark; if too short a time, they show too pale. For this reason the tissues should be examined before they are passed from the reducing solution to water. Fresh material gives the best pictures, but I also obtained good results from old material.

With this comparatively simple method, Stöhr, Jr.,[4] followed the nerve supply of the blood vessels of the pia, the choroid plexus of the third and fourth ventricles, and of some visceral organs. The pictures so stained are striking. Figure 1, for instance, represents the nerves of a minute artery (0.12 mm.) of the peduncular pia from a dog's brain. The nerve appears here as a curved, varicose, zigzagged thread accompanied by the nuclei of Schwann. The latter usually run parallel to the nerve fibers; often they are closely adjacent to them, flattened and thinned. They are of large size, rich in chromatin and widely separated from one another. In some instances, the nerve fibers are bordered by or enclosed within broad granular brownish bands (fig. 2). These often appeared as thick granular fibers, freely scattered; or they could be traced to large cell bodies (fig. 3) which also were granular, possessing a large pale nucleus, a nucleolus and numerous branching processes. The cells showed as multipolar stellate bodies; some were spindle shaped and their nuclei were oblong and flattened. Whatever the form and size, their processes did not form anastomoses. The cell bodies were much larger than ganglion cells, which they resemble, but they possessed no fibrils and generally appeared as massive, rather coarse structures. These cell bodies are the so-called chromatophores, pigment-producing connective tissue cells. They were especially numerous in the basal pia of the brain where, as noted, there is also an abundance of sympathetic nerve fibers. As figure 2 shows, the cells are present also in the walls of the blood vessels themselves. Among these cells and their processes one sees the nerve fibers winding along, running parallel to the long axis of the blood vessel and sometimes blending with or enveloped by them (fig. 2).

The fibers can be recognized by their dark color, by varicosities and, in many instances, by the accompanying nuclei of cells of Schwann. Often the nerve fibers traveled together. In figure 4, a set of eight fibers is seen running parallel, all devoid of myelin and some of them

4. Stöhr, Jr., P.: O. Schultze's Natronlauge—Silber-Methode zur Darstellung der Achsencylinder und Nervenzellen, Anat. Anz. **54**:529, 1921; Ueber die Innervation der Pia mater und des Plexus choroideus des Menschen, ibid., page 55, and Ztschr. f. Anat. u. Entwcklngsgesch. **63**:562, 1922; Ueber die Innervation der Pialscheide des Nervus opticus beim Menschen, Anat. Anz. **55**:298, 1922; Beobachtungen über die Innervation der Pia mater des Rückenmarks und der Tela chorioidea beim Menschen, Ztschr. f. Anat. u. Entwcklngsgesch. **64**:555, 1922; Nerven der Blutgefässe, in Müller, L. R.: Die Lebensnerven, Berlin, Julius Springer, 1924; Mikroskopischer Beitrag zur Innervation der Blutcapillaren beim Menschen, Ztschr. f. Zellforsch. u. mikr. Anat. **3**:431, 1926; Die peripherischen Anteile des vegetativen Nervensystems, in Möllendorf, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4, part 1, p. 265.

exhibiting marked varicosities. Such are especially well seen in single nerve fibers (fig. 1) and their branches. Other nerve fibers formed a network (fig. 5) or plexuses of nonmedullated fibers. These were mainly periadventitial, as they could easily be discerned over the adventitia. Though also present (fig. 6) in the muscle tunic, they were here much more difficult to show. Some nerve fibers here were minute, thin and granular twigs running as dotted lines (fig. 7) parallel to the nuclei of the muscle cells which they sometimes enveloped. In

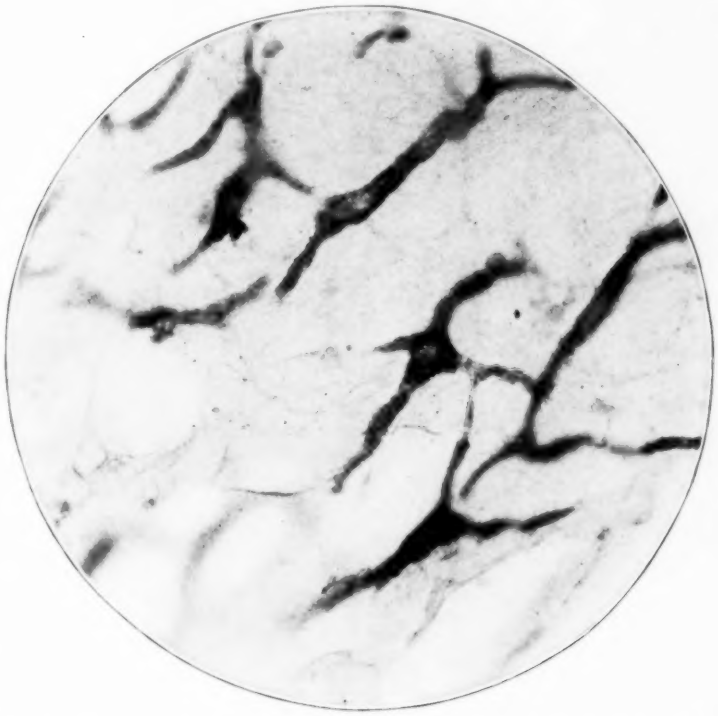

Fig. 3.—Chromatophore cells—explanation in text (dog's brain). Schultze-Stöhr method counterstained with Alzheimer-Mann stain; × 680.

still rarer instances, the vessel walls contained formations much resembling ganglion cells (fig. 8). The cell body and the narrow portion corresponding with the site of the nucleus were rather densely stained and their processes were paler, but, like the cell body, they appeared homogeneous and structureless.

It was not possible to establish the connection of the fibers with the vessel wall, that is to say, the mode of their termination. As a matter of fact, it was not always easy to follow the end-stations of the vascular

nerve fibers. As a rule, these could be followed over a long stretch, down to the smallest branches. Here (fig. 9) they were represented by a thin black curved thread extending over the wall. It terminated sometimes in bulblike, knoblike or nodular enlargements (figs. 9 and 10). In other rarer instances the terminations were as convolutions of nonmedullated nerve fibers, with end-platelets as pictured in figure 8. Like the thin granular fibrils seen in figure 7, the foregoing formations were most likely the endings of vascular nerve fibers.

Fig. 4.—The adventitia of a small blood vessel (0.34 mm.) is crossed by a bundle of eight nerve fibers, some of which exhibit marked varicosities (dog's brain). Staining and magnification as in figure 1.

The observations described were all made on the pia of the base of the brain—over the pons, cerebellum, medulla and peduncles of the brains of man, dogs, guinea-pigs and rabbits. The pia of the cortex of the brain also showed the presence of the vascular nerves, but over the convexity of the brain the pial blood vessels were practically devoid of them. In the gray and white substances they were absent entirely. None could be found even in the pial prolongations between the convolutions.

SUMMARY OF HISTOLOGIC OBSERVATIONS

The pial blood vessels, excepting the capillaries, possess a wealth of nerve fibers within the adventitial and muscular layers. Some fibers are medullated; the majority are naked and represented by varicose threads; they run singly or in bundles; occasionally, they give off branches and form networks. The fibers show free endings in the adventitia, in the form of bulbs; in the muscle layer the endings are less definite. The vascular nerves are generally abundant at the base

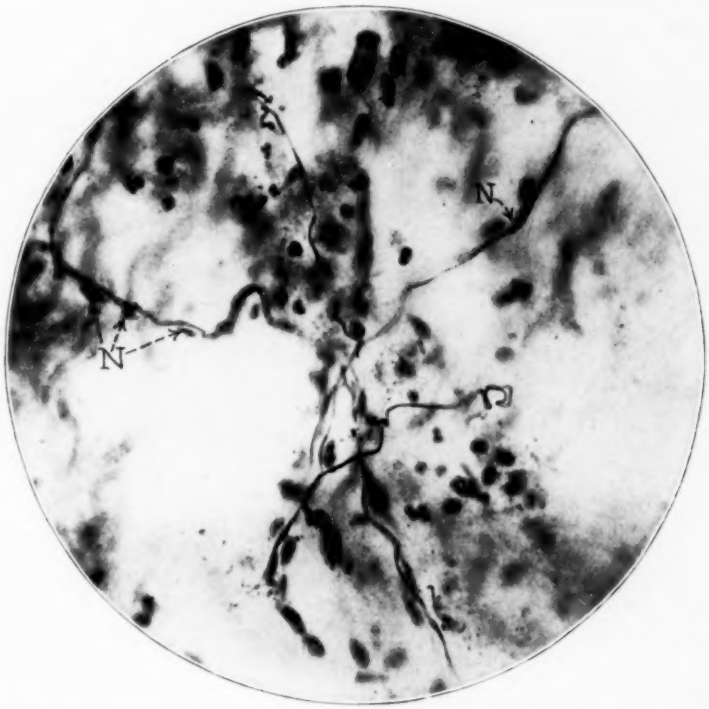

Fig. 5.—Network of vascular nerve fibers (size of the blood vessel 0.6 mm.). The fiber to the right (*N*) is covered with myelin and shows several Schwann cells (dog's brain). Schultze-Stöhr method; × 420.

of the brain, where they are often mixed with so-called chromatophore cells; no nerve fibers were found in the blood vessels of the brain substance itself.

COMMENT

The observations here recorded are essentially analogous to those of Stöhr, Jr. In a number of brilliant contributions [4] he showed that the blood vessels of the pia and the choroid plexus possess a wealth

Fig. 6.—Network of nerve fibers on the muscularis; dog's brain (peduncular pia). Size of the blood vessel 0.6 mm. Schultze-Stöhr method; × 280.

of nerve fibers. Partly confirmed by Berger,[5] Stöhr's observations may be considered the only proof of the presence of nerve fibers in the pial blood vessels. It is true that a number of older investigators—Retzius,[6] Obersteiner,[7] Morrison,[8] Huber,[9] Gulland,[10] Hunter[11] and others—described formations which they considered nerve fibers. Of these, only Retzius and, to some extent, Huber seem to have furnished convincing descriptions. In the arteries of the choroid plexus of a white rabbit Retzius found muscle cells that contained finest threads in the form of varicose terminations. The periarterial nerve plexuses not only formed nets, but also emitted here and there varicose branches which lay adjacent to the muscle layer of the arterial wall, terminating free. Yet even Retzius' observations differ from those recorded here; Stöhr stated that the observations of other investigators, including even those of Huber, resembled little those described by himself.

A few words should be said in reference to the chromatophore cells. As stated, they much resembled ganglion cells. The latter are occasionally seen in the choroid tela, in the pia and, according to Stöhr, in the deeper adventitia, between the latter and the media. They are much less common than the chromatophores which in my specimens were conspicuous by their huge size, the enormous length of their processes, the granular appearance and the absence of a fibrillary structure. Their significance is not clear. Nor is it possible to account for their prevalence in areas rich in sympathetic nerve fibers, or for the occasional presence of the latter within their processes. Whatever their nature, they certainly have nothing to do with the innervation of the intracranial blood vessels. These possess a definite neuromuscular apparatus, the activity of which is responsible for the changes in the lumen of the blood vessels—their contraction and dilatation. It was assumed that a similar mechanism is present also in the capillaries and precapillaries, regardless of the fact that these possess neither muscle cells nor nerve fibers. It is true that the latter may be seen on the capillary wall, but without giving off branches or exhibiting endings.

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5. Berger, H.: Zur Innervation der Pia mater und der Gehirngefässe, Arch. f. Psychiat. **70**:216, 1924.

6. Retzius, G.: Biol. Untersuch. **3**:52, 1892.

7. Obersteiner, H.: Die Innervation der Gehirngefässe, J. f. Psychiat. u. Neurol. **16**:215, 1897.

8. Morrison, A.: On the Innervation of Intracranial Vessels, Edinburgh M. J. **4**:413, 1898.

9. Huber, C.: Observations on the Innervation of the Intracranial Vessels, J. Comp. Neurol. **9**:1, 1899; Lectures on the Sympathetic Nervous System, ibid. **7**:73, 1897.

10. Gulland, L.: The Occurrence of Nerves on Intracranial Blood Vessels, Brit. M. J. **2**:780 (Sept. 17) 1898.

11. Hunter, William: On the Presence of Nerve Fibers in the Cerebral Vessels, J. Physiol. **26**:465, 1901.

One may also assume that the minute blood vessels and the capillaries are utilized by the nerve fibers as conducting pathways or that they accidentally intermingle. Some investigators, however, hold that the association of or the connection between the capillaries and the sympathetic nerve fibers is not an accident but is a definite neuromuscular structure. Its neural component is the sympathetic nerve; the muscular component is represented by so-called Rouget cells or pericytes (Zimmermann,[12] Ebbecke[13]). The latter, stimulated by the sympathetic nerve fibers, cause contraction of the capillaries (Krogh[14]). The

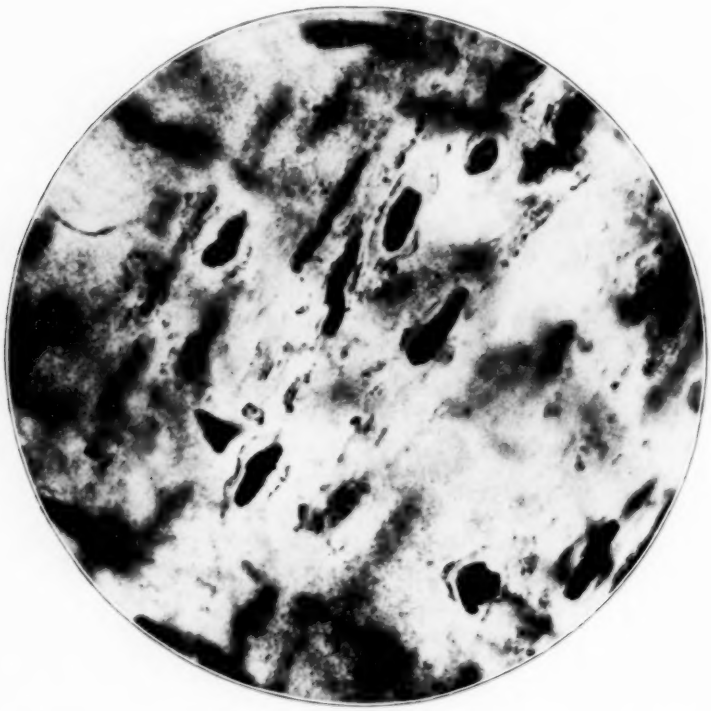

Fig. 7.—Human brain. Muscle tunic of a small blood vessel. The black bodies are nuclei of the muscle fibers, in many instances surrounded by delicate granular nerve fibers. These are evidently the terminal branches. Size of blood vessel 0.14 mm. Schultze-Stöhr method; × 780.

12. Zimmermann, K. W.: Der feinere Bau der Blutkapillaren, Ztschr. f. Anat. u. Entwcklngsgesch. **68**:29, 1923.

13. Ebbecke, U.: Physiologie der Capillaren, Naturwissenschaften **14**:1131, 1926.

14. Krogh, A.: Anatomie und Physiologie der Capillaren, German translation by Ebbecke, Berlin, Julius Springer, 1924; Die Capillarnerven und ihre reflectorische Tätigkeit, Klin. Wchnschr. **6**:722 (April 16) 1927.

changes observed by Golubew,[15] Tarchanoff,[16] Rouget,[17] Steinach and Kahn [18] in the walls and lumina of the capillaries in the larvae of amphibia or in older animals have been ascribed by Krogh also to the presence and activity of the foregoing cells. Vimtrup [19] described them as situated outside the capillary wall, over the "endothelial" membrane; they are more massive than the endothelial cells; they are round or oblong; their axis is parallel to the long axis of the blood vessel; the nuclei are enveloped by a cytoplasm which thins out into sharp processes. These run parallel to the capillary, but they envelop it with their processes, which may be numerous and cause not only its contraction but even its complete obliteration. Krogh and his pupils concluded that these contractile cells of the capillary wall cause an independent activity of the capillaries; that the entire vascular system of the brain is thus provided by a nerve apparatus which controls the cerebral circulation, and that the capillaries possess a tonus of their own, exhibiting phenomena of contraction and relaxation.

While it cannot be denied that so-called Rouget cells are present in the larvae of amphibia, they were not found in the adult amphibia or in mammals, though Krogh [14] stated, somewhat vaguely, that they were found also in mammals (in the connective tissue and the blood vessels of the skin). Even in the larvae, however, these cells are not muscular, but mesenchymal, as was, in my opinion, conclusively proved by E. R. Clark and E. L. Clark.[20] I wish to state that one may see such cells in the capillaries of any brain, including that of man. Figure 11, for instance, shows a minute capillary, just wide enough to harbor only one red blood corpuscle. The lumen of the capillary exhibits at *E-E* thin, flattened, endothelial cells. Outside the lumen, over the endothelial membrane, a different type of a nucleus—peri-endothelial—(at *R*) is present. It is larger and enveloped by a thin membrane (*M*). Its aspect and position

15. Golubew, A.: Beiträge zur Kenntniss des Baues und der Entwicklungsgeschichte der Capillargefässe des Frosches, Arch. f. mikr. Anat. **5**:49, 1869.

16. Tarchanoff, I.: Beobachtungen über contractile Elemente in den Blut und Lymphcapillaren, Pfluger's Arch. f. d. ges. Physiol. **9**:407, 1874.

17. Rouget, Charles: Mémoire sur le développement, la structure et les propriétés physiologiques des capillaires, Arch. de physiol. norm. et path. **5**:603, 1873; Sur la contractilité des capillaires sanguins, Compt. rend. Acad. d. sc. **88**:916, 1879.

18. Steinach, E., and Kahn, R.: Echte Contractilität und motorische Innervation der Blutcapillaren, Arch. f. d. ges. Physiol. **9**:105, 1903.

19. Vimtrup, B.: Beiträge zur Anatomie der Capillaren; über contractile Elemente in der Gefässwand der Blutcapillaren, Ztschr. f. Anat. u. Entwcklngsgesch. **65**:150, 1922.

20. Clark, E. R., and Clark, E. L.: The Relation of "Rouget" Cells to Capillary Contractility, Am. J. Anat. **35**:265, 1925; The Development of Adventitial (Rouget) Cells on the Blood Capillaries of Amphibian Larvae, Am. J. Anat. **35**:238, 1925.

correspond exactly with what Rouget, S. Meyer [21] and especially Vimtrup described as Rouget cells which, as pointed out, constitute in their opinion the muscular apparatus of the vascular capillary system. The absence here (fig. 11) of the processes which are usually abundant in Rouget cells may be due to the time element, for, as Clark and Clark [20] showed, the "branched processes of the stellate connective tissue cells are gradually withdrawn as its protoplasm flattens out on the endothelial tube. It remains permanently flattened out on the outer wall of the capillary, definitely distinguishable from its endothelium."

Fig. 8.—Adult human brain. The large round mass (*G*) in the lower portion of the picture is evidently a ganglion cell with dentrons; the broad pale band to the left is a chromatophore (*Chr.*) process; at *Conv.* is a convolution of nerve fibers enclosing pale, round cells forming an end-platelet; the solid dark lines are nerve fibers. The majority of the nuclei are Schwann cells (size of the blood vessel, 0.33 mm.). Schultze-Stöhr method; × 540.

Even if it is assumed that the cells in question are muscle cells, their anatomic connection with the nerve fibers would be altogether unconceivable. The entire length of the adventitia (fig. 12) of the

21. Meyer, S.: Die Muscularisierung der capillaren Blutefässe. Nachweis des anatomischen Substrats ihrer Contractilität, Anat. Anz. **21**:442, 1902.

capillary is taken up by or covered with the footlets of the macroglia (cytoplasmic and fibrous glia.) Were the capillaries supplied with nerve fibers these would not even reach the adventitia, but would end in the periadventitial glia. The space separating the latter from the adventitia is generally considered an artefact, and is also described as a shrinking space or as a space of His. In the picture it is traversed by numerous threads connecting the adventitia with the surrounding parenchyma. Were the walls of the capillary supplied with nerve fibers, the latter would be seen traversing the periadventitial spaces. This is not the

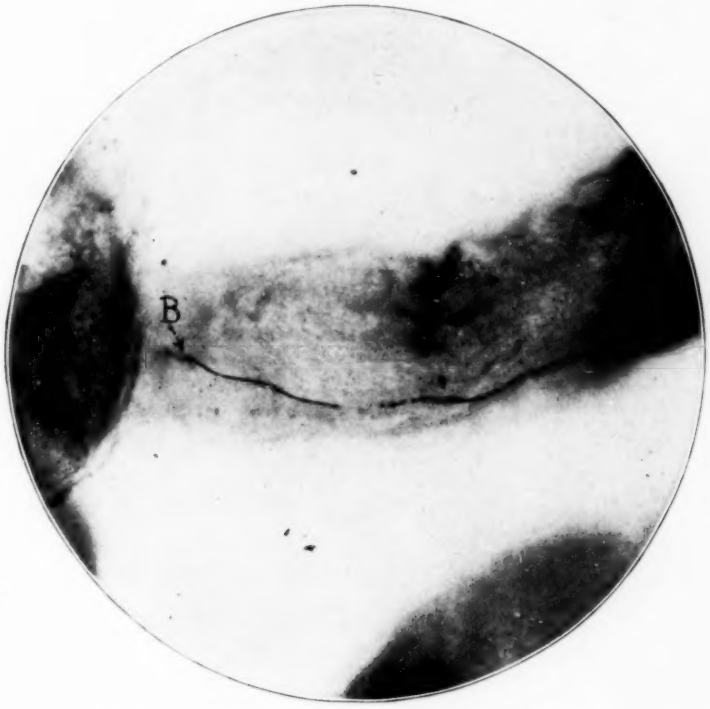

Fig. 9.—Adult human brain. A nonmedullated nerve fiber on a small blood vessel (0.1 mm.) ending in a bulb (*B*). Schultze-Stöhr method; × 540.

case, however, for the foregoing threads are parts of the glia processes. It is probable that such footlets have been mistaken by Hunter and others for ganglion cell processes which, in their opinion, innervate the cerebral blood vessels.

It was also suggested that the nerve fibers, after leaving the pia or branching off from the larger nerves of the pia, merely run alongside the capillaries, accompanying them. Such an assumption is altogether illogical, mainly because of the enormous masses of capillary blood

vessels in the brain (fig. 13). Here the capillary networks are denser than elsewhere in the body (Lorente de Nó [22]), the meshes being just large enough to make room for only one ganglion cell, while, according to Krogh, in a small mammal, 1 sq. mm. harbors more than 4,000 capillaries. If these possess nerve fibers at all, they must be derived from the nerves of the pia. As these are themselves microscopically small, though abundant, they would be decidedly insufficient to provide myriads of capillaries and other blood vessels of the brain even with the tiniest threads. It is evident that capillary innervation is an

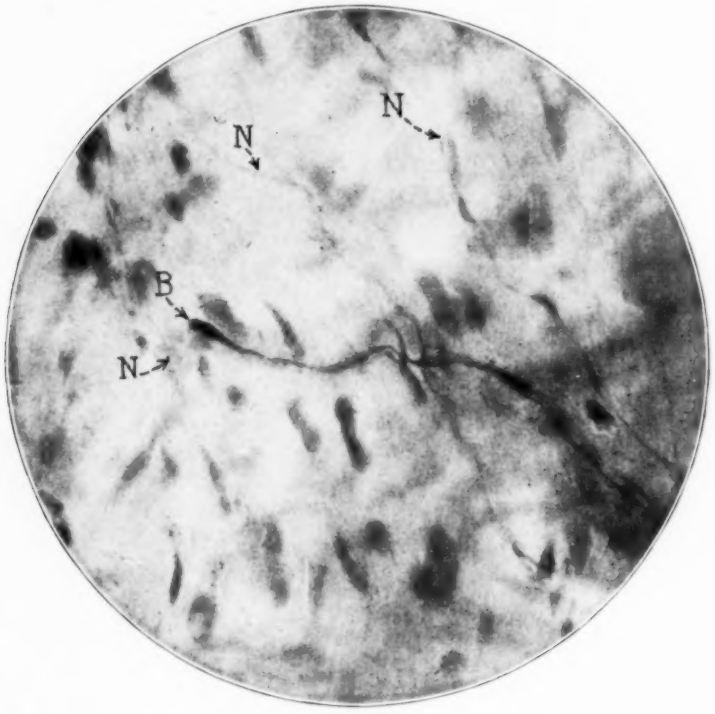

Fig. 10.—Several nerve fibers (*N*) of the muscularis; one exhibits a terminal bulb (*B*). Stain and magnification as in figure 1.

anatomic impossibility. Physiologically, it is not necessary, for Roy and Graham Brown,[23] Roy and Sherrington,[24] Bayliss and Hill,[25]

22. Lorente de Nó, R.: Ein Beitrag zur Kenntniss der Gefässvertheilung in der Hirnrinde, J. f. Psychol. u. Neurol. **35**:19, 1927.

23. Roy, Charles; and Graham Brown, J.: The Blood-Pressure and its Variation in the Arterioles, Capillaries and Smaller Veins, J. Physiol. **2**:323, 1879-1880.

24. Roy, Charles; and Sherrington, C. S.: On the Regulation of the Blood Supply of the Brain, J. Physiol. **11**:85, 1890.

25. Bayliss, M., and Hill, Leonard: On Intracranial Pressure and the Cerebral Circulation, J. Physiol. **18**:334, 1895.

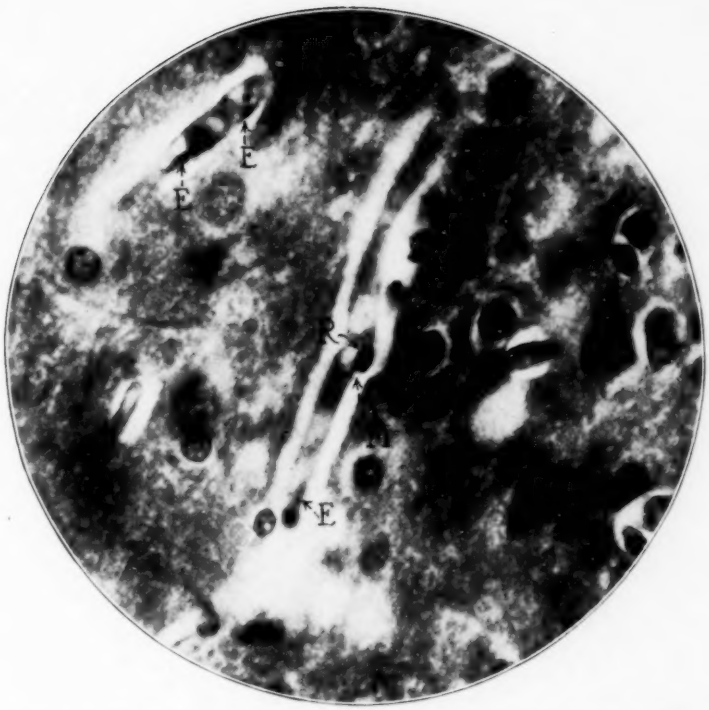

Fig. 11.—A capillary. At *E*, endothelial cells; at *R*, a so-called Rouget peri-endothelial or adventitial cell, enveloped by its processes, *M*. Alzheimer-Mann stain; × 600.

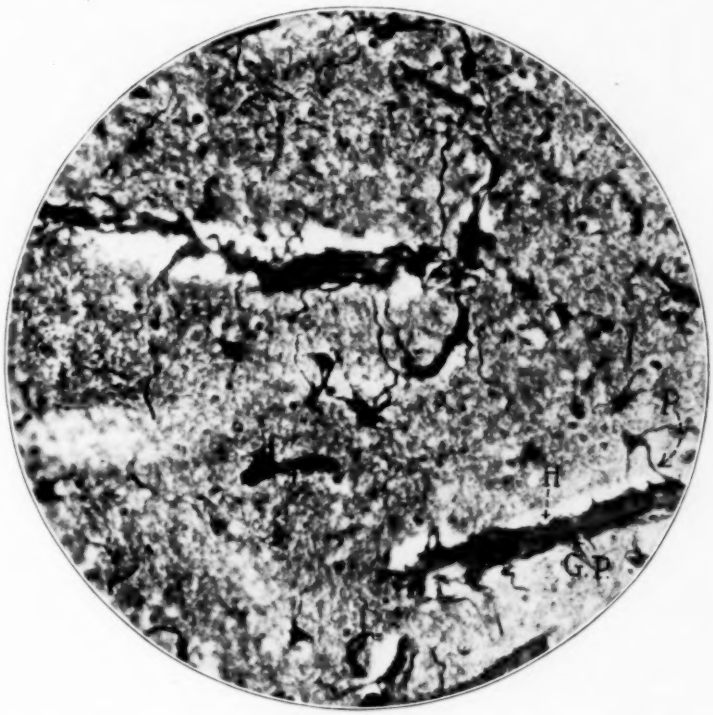

Fig. 12.—The processes of macroglia cells (*P*) are seen attached to and extending (at *G.P.*) along the adventitia of a capillary. As thin fibrils they bridge the space (*H*) between the adventitia and the parenchyma (at *P*). No other formations, such as nerve fibers, can be detected. Cajal gold corrosive sublimate stain; × 380.

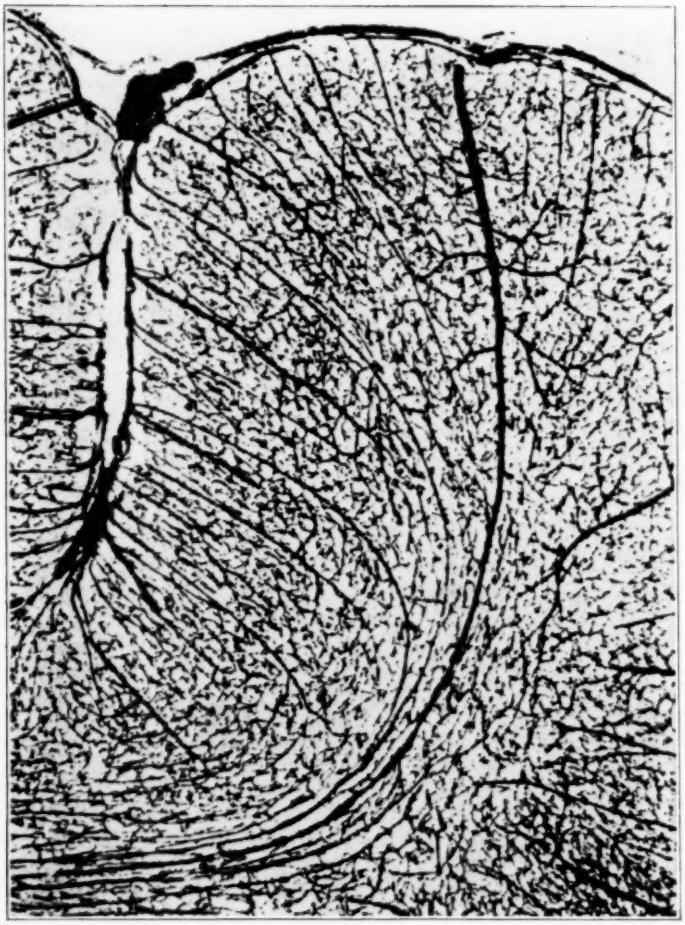

Fig. 13.—Vascular supply of a cortical area (from Pfeiffer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928).

Langley [26] and others showed that contraction of the capillaries may be brought on by chemical and other factors. Lately, for instance, Nesterow [27] pointed out that the innervation and activity of the precapillary arteries which are under the constant control of the central nervous system are sufficient to explain the phenomena which characterize the capillary blood circulation, and that the active contraction of the capillary walls is unnecessary. Ohno [28] is of a somewhat similar opinion. Some investigators, as Rohnstein,[29] even go so far as to deny altogether the existence of nerve fibers even on the walls of the larger blood vessels of the pia, while other investigators, such as E. Weber [30] and Lorente de Nó,[22] hold that the blood circulation may be regulated by the glia cells through their processes attached to the adventitia. It would thus seem reasonable to agree with the physiologists (Leonard Hill, Roy and Sherrington,[24] Bayliss) that the cerebral blood vessels proper do not possess nerves. They, however, are abundant in the pial blood vessels, which not only supply their cerebral branches with blood but seemingly also control, indirectly, their activity.

CONCLUSIONS

1. The blood vessels of the pia are rich in nerve fibers.

2. The vascular nerve fibers may be single, or in bundles; they are mostly naked, that is, devoid of a myelin cover.

3. The blood vessels of the cerebral parenchyma, as well as the pial capillaries, are devoid of nerve fibers.

4. The nerve fibers are especially abundant at the base of the brain where they are mixed with chromatophores.

5. The pia dominates the cerebral circulation not only by supplying the vessels with blood, but also, partly at least, by controlling their activity (contraction and dilatation).

6. The cells of the adventitia of the cerebral capillaries are practically identical with so-called Rouget cells. These are not muscle, but connective tissue cells and have nothing to do with the capillary innervation.

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26. Langley, J. N.: Antidromic Action, J. Physiol. **58**:49, 1923.

27. Nesterow, A. J.: Ueber Contractilität der Blutcapillaren beim Menschen, Arch. f. d. ges. Physiol. **209**:465, 1925.

28. Ohno, Y.: Beiträge zur Frage der neuropathologisch. Entzündungslehre, Beitr. z. path. Anat. u. z. allg. Pathol. **72**:722, 1924.

29. Rohnstein, R.: Zur Frage nach dem Vorhandensein von Nerven an den Blutgefässen der grossen Nervencentren, Arch. f. mikr. Anat. **55**:576, 1900.

30. Weber, E.: Ein Nachweis von intrakraniell verlaufenden gefässerweiternden und verengernden Nerven für das Gehirn, Zentralbl. f. Physiol. **21**:237, 1907; Ueber die Selbständigkeit des Gehirns in der Regulierung seiner Blutversorgung, Arch. f. Anat. u. Physiol., Physiol. Abth., 1908, p. 456.

Society Transactions

THE ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

Ninth Annual Meeting, Dec. 27-28, 1928

WALTER TIMME, M.D., *President*

The subject discussed at this meeting was "The Vegetative Nervous System." The following program was presented.

AN HISTORICAL RETROSPECT OF THE VEGETATIVE NERVOUS SYSTEM.

Presidential Address, DR. WALTER TIMME, New York.

MORPHOLOGY

DEVELOPMENT OF THE AUTONOMIC NERVOUS SYSTEM. DR. ALBERT KUNTZ, St. Louis.

THE DIVISIONS OF THE VEGETATIVE NERVOUS SYSTEM WITH ITS GANGLIA AND PLEXUSES: PERIPHERAL DISTRIBUTION OF THE VARIOUS PARTS OF THE VEGETATIVE NERVOUS SYSTEM. DR. ANGUS MCDONALD FRANTZ, New York. (To be published but not presented.)

THE CENTRAL REPRESENTATION OF THE SYMPATHETIC SYSTEM: AS INDICATED BY CERTAIN OBSERVATIONS. DR. PHILIP BARD, Princeton, N. J.

FUNCTIONAL SIGNIFICANCE OF HISTOLOGIC CHARACTER IN PREGANGLIONIC VISCERAL NEURONS. DR. E. F. MALONE, Cincinnati.

DISTRIBUTION OF SYMPATHETIC AND DORSAL ROOT FIBERS THROUGH GRAY RAMI. DR. ALBERT KUNTZ, St. Louis.

THE INNERVATION OF THE MUSCLE SPINDLE. DR. MARION HINES, Baltimore.

OBSERVATIONS ON THE INNERVATION OF THE BLOOD VESSELS IN SKELETAL MUSCLE. DR. JOSEPH C. HINSEY, Chicago.

PHYSIOLOGY

THE SYMPATHETIC DIVISION OF THE AUTONOMIC SYSTEM IN RELATION TO HOMEOSTASIS. DR. WALTER B. CANNON, Boston.

SOMATIC AND VISCERAL CONNECTIONS OF THE DIENCEPHALON. DR. G. CARL HUBER and DR. ELIZABETH C. CROSBY, Ann Arbor, Mich.

THE RELATION OF THE INTEGRITY OF THE SYMPATHETIC NERVOUS SYSTEM TO THE CARDIAC ARRYTHMIAS PRODUCED BY CHLOROFORM ANESTHESIA. DR. G. R. BROW, Montreal, Canada.

THE SYMPATHETIC NERVOUS SYSTEM AND ITS RELATION TO CARBOHYDRATE METABOLISM. DR. C. N. H. LONG, Montreal, Canada.

THE HYPOTHALAMUS AND ITS RELATION TO THE SYMPATHETIC NERVOUS SYSTEM. DR. J. BEATTIE, Montreal, Canada.

TONUS IN SKELETAL MUSCLE IN RELATION TO SYMPATHETIC INNERVATION. DR. ALEXANDER FORBES, Boston.

THE INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON THE CAPILLARIES DURING PERIPHERAL STASIS. DR. J. HAMILTON CRAWFORD, Brooklyn.

ENDOCRINE GLANDS AND THE AUTONOMIC NERVOUS SYSTEM. DR. R. G. HOSKINS and DR. M. O. LEE, Boston.

VASCULAR INNERVATION OF THE THYROID. DR. JOSE F. NONIDEZ, New York.

EXPERIMENTAL INVESTIGATION

THE DISPENSABILITY OF THE SYMPATHETIC NERVOUS SYSTEM. DR. ROBERT M. MOORE, Boston.

THE PARASYMPATHETIC CONTROL OF MUSCLE TONUS. DR. S. W. RANSON, Chicago.

THE REGENERATION OF SYMPATHETIC NERVE FIBERS. DR. FERDINAND C. LEE, Baltimore.

THE NERVE SUPPLY OF THE CEREBRAL BLOOD VESSELS: A HISTOLOGIC STUDY. DR. GEORGE B. HASSIN, Chicago.

THE RELATIONSHIP OF THE CERVICAL SYMPATHETIC NERVES TO CEREBRAL BLOOD SUPPLY. DR. STANLEY COBB, Boston.

VAGUS NERVE ACTIVITY IN RELATION TO THE CARDIAC AND PYLORIC SPHINCTERS: ANIMAL INVESTIGATION. DR. WALTER HUGHSON, Baltimore.

CLINICAL INVESTIGATION

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SECOND CONGRESS OF THE FRENCH SOCIETY FOR OTONEURO-OPHTHALMOLOGY

Marseille, May 25 and 26, 1928

H. ROGER, *President, in the Chair*

VASCULAR SPASM IN OTOLOGY. PROF. G. PORTMANN.

This (as well as the other two principal papers) has been published in the *Revue d'Oto-Neuro-Ophtalmologie*, 1928, vol. 6. Dr. Portmann began by discussing the physiology of the vessels to the external ear, the middle ear and the internal ear, saying that normal blood supply to these parts depends directly on the periarterial and cervical sympathetic nerves, and on the regulation of the general circulation. In the middle ear the most common symptom of angiospasm is tinnitus; this is indicated by the fact that the symptom disappears with the vasodilatation following sympathectomy. Much experimental work has been done, and it has been proved that the cervical sympathetic has a vasomotor control over the vessels of the labyrinth, the hypervascularization following sympathectomy causing hypo-excitability of the vestibular apparatus. Pericarotid sympathectomy has a similar effect, largely unilateral. The reaction to vasomotor drugs was described; epinephrine caused hyperexcitability of the vestibule, while ergotin, eserine, pilocarpine, atropine and amyl nitrite caused lowering of excitability. This is in line with the general action of these drugs on sympathetic nerves.

From the clinical standpoint, phenomena due to vasomotor abnormality in the external ear are erythrosis, pruritus of the lobule, ceruminous hypercrinia and herpes. These may be associated with Raynaud's disease, erythromelalgia or acrocyanosis. Little is known of the reactions of the middle ear to such diseases. The internal ear responds with vertigo, tinnitus and deafness. A good bibliography accompanies the published paper.

VASCULAR SPASM IN NEUROLOGY. F. BREMER, Brussels.

This was a brief paper, summarizing some of the recent work and giving a short list of references. It is concisely stated and gives the author's point of view. He feels that no real proof has yet been shown anatomically to justify the clinical concept of angiospasm of the nerve centers. Nosologically, the justification for the term depends on: (1) the association of the central nervous system symptoms with peripheral angiospastic phenomena; (2) the efficacy of vasodilator drugs; (3) the impossibility of otherwise explaining symptoms that are so well explained by supposing a transitory arterial occlusion. Taking up the anatomic details he states that cortical arteries, those that arise from the circle of Willis and the intramedullary arteries are terminal. [Pfeifer's recent work disproving this is not mentioned — Ed.] The question of innervation is discussed; Stöhr's

anatomic demonstration of innervation of the arteries of the pia mater is quoted, but "this presence of nerve fibers in the vascular walls does not constitute a proof of vasomotor innervation of the vessels, for the existence of a sensory vascular innervation has been demonstrated." There is evidence that, like all smooth muscle, vessel walls contract when directly stimulated. The work of Florey and others is quoted to show that there is probably no vasomotor innervation, or at best a very feeble innervation of the cerebral pial vessels.

Taking up the symptomatology of cerebral angiospasm, Bremer accepts the general opinion that ischemia does take place in the brain on the basis of arterial contracture, and speaks even of partial ischemias of the cortex, thalamus, etc. In general the symptoms are characterized by the suddenness of their appearance, brevity of their duration, variability of location and absence of sequelae. Provisionally he divides the etiologic factors into: (1) visible alteration in the vessel walls; (2) Raynaud's disease; (3) toxins as nicotine, lead, quinine and ergot; (4) endogenous intoxications (nephritis, hypertension, biliary migraine); (5) essential migraine; (6) reflex. A good description of these various clinical entities is given, with references to the principal authors. The last catagory — reflex angiospasm — is the least well proved. Migraine is the commonest; it is probably due to humoral changes; the common conception of vasomotor spasm is not easy to support if one believes that there is no innervation of the deep cortical arteries. "Angiospasm is the contracture, that is to say, the momentary exaggeration of tonus, of a smooth muscle. This tonus is at each instant the resultant of a multitude of more or less independent variables," for example: (1) the intrinsic properties of the muscle fiber; (2) temperature; (3) chemical composition of the internal environment; (4) vasomotor activity. The importance of the last is usually exaggerated at the expense of the more important others. "Without denying absolutely the possibility of reflex cerebral angiospasm, I believe them to be very exceptional and limited to the gross arterial trunks." "The hypothesis that the epileptic attack is caused by angiospasm is merely a conception too simple to be worth discussion."

Treatment of these conditions is symptomatic, and consists of using drugs with a calming effect, and vasodilators — for example benzyl benzoate, papaverine, trinitrine, nitrites, phenobarbital and bromide.

In conclusion the author says: "The etiologic factors are diverse; there are: (1) Angiospasms from local arteritis, these are perhaps the least well established. (2) Toxic angiospasms with episodic symptoms indicating endogenous or exogenous intoxication, acting on normal vessels or making a tendency for vessels to react spasmodically to various causes. (3) The other angiospasms are apparently the expression of a constitutional spasmophilia. These are seen in Raynaud's disease and its 'formes frustes' with their angiospastic phenomena capriciously scattered or electing the extremities; also in migraine where there are vasomotor phenomena almost always cephalic.

Certain syndromes characterized by the extreme frequency of cerebral and peripheral angiospasms, associated or alternating, are difficult to classify.

The rôle of the vasomotor nerves in the pathogenesis of most angiospasms of the central nervous system is of doubtful importance; this is because of the insignificance or even complete absence of vasomotor innervation to the cerebral and medullary arteries, especially their terminal branches.

The exogenous poisons such as lead, quinine and nicotine are spasmogenic through their direct action on the smooth muscle fibers. There is probably a similar but as yet unknown mechanism for the nephritic angiospasms.

The pathogenesis of the attacks in Raynaud's disease and migraine is still mysterious. Certain facts allow an analogy between these attacks and those of anaphylactic shock.

The treatment of angiospasms of the nerve centers is etiological and symptomatic (vasodilator). Its efficacy is very variable."

DISCUSSION

Dr. Barré, Strasbourg: One should not identify spasm with contraction — spasm has different degrees and does not always cause anemia or ischemia. The

study of vascular spasm should not be limited to the observation of arterial tension, but the blood supply, the actual flow, is important.

Dr. Tournay, Paris: After hearing the report of Dr. Bremer one should be careful about exaggerating the importance of the vasomotor nerves, but one might well ask just how far the nervous system could be ignored. I wish to mention the work of Lennox and Cobb on epilepsy, and of Forbes and Wolff on vasomotor control of the cerebral vessels, who have presented evidence to show that the cerebral circulation is regulated not only from a distance by changes in general blood pressure, but also by a vasomotor mechanism in the cerebral vessels themselves. Kubie's work corroborated that of Forbes and Wolff and showed that the vessels of the cortex might act differently from those of the pia. One can say only that the question of cerebral vascular caliber is at present open to investigation. The best explanation of the pathologic phenomena is a combination — a theory that envisages a neurohumoral vicious circle.

Dr. Ferrari, of Rome, insisted on the active character of vasodilatation, saying that it was not produced merely by inhibition.

Dr. Bremer: The physiology and pathology of the cerebral and retinal vessels present a remarkable similarity. I rejected the angiospastic pathogenesis of epilepsy and epileptic equivalents because of the absence of sequelae, an absence which contrasts with their frequency in true angiospastic syndromes, in migraine for example.

Vascular Spasm in Ophthalmology. Dr. Aubaret and Dr. Sedan.

The authors begin with a review of the early work of Pourfour du Petit, in 1712, and of Claude Bernard, in 1851, describing the well known effects of cutting the cervical sympathetic as observed by Bernard, resulting in myosis, enophthalmos, narrowing of the palpebral fissure and conjunctival hyperemia. In 1869, Horner observed, in addition, hypotonia of the eyeball and hyperemia of the retina. The experimental and clinical work is then reviewed briefly up to the recent advances made by Leriche. All these experiments and observations indicate that the vessels of the retina have vasomotor changes of a much lesser degree than those found in other parts of the body. On the other hand, chemical substances cause marked changes in the retinal vessels; for example, amyl nitrite and epinephrine. The interesting observations of Baillart are recounted. He injected into a normal eye two drops of 1/1000 epinephrine solution. The patient immediately reported a "multitude of stars" appearing. Five minutes later the intra-ocular pressure had risen from 18 to 90 mm. The vessels of the retina were contracted and the arterial pulse appeared. With this the visual acuity fell to 1/20. Twelve minutes later, the intra-ocular pressure had returned to 26. Other authors have observed that retrobulbar injection of epinephrine and procaine hydrochloride causes an ischemia of the choroid and of the iris, but no alteration in the vessels of the retina. These and numerous other observations have led to a lively discussion among ophthalmologists concerning the innervation of the vessels of the retina. One group believes that the retinal arteries are not affected by sympathetic stimulation because they emanate from the arteries of the brain. The other group believes that sympathetic stimulation reaches all parts of the body. This also brings up the question as to whether the spasms of the arteries observed with the ophthalmoscope are not due to direct effects on the walls of the vessels without the intervention of the sympathetic nerves. Numerous authors are quoted in this regard.

From the clinical standpoint the authors discuss ocular angiospasm, describing the main symptom as a sudden clouding of vision usually unilateral, never complete, and rarely hemianopic. There are two varieties: one affects the whole of the central artery and the other only branches. Numerous cases are quoted and the references given. Angiospasm may also be associated with lesions of the retina or of the optic nerve. Spasms have been observed in the choroid and in the ciliary body as well as in the iris.

In regard to epilepsy they quote various men who have observed vasoconstriction in the retina at the beginning of an attack. Cantonnet, in 1914, observed a retinal spasm in which all the arteries contracted fifteen seconds before the onset of the convulsion, and then fifteen seconds before the end of the convulsion all the vessels returned to normal caliber. Cases are also quoted in which absolute blindness followed an epileptic attack. The vision returned to normal the next day. It has also been observed that after an epileptic attack the visual fields may be constricted or there may be scotomas. They believe, therefore, that epilepsy is a common cause of angiospasm of the retina. Other causes are the use of quinine, tobacco and alcohol.

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O. FOERSTER, M.D., *President*

DEUTSCHE ZEITSCHRIFT FUR NERVENHEILKUNDE **106**:109 (Dec.) 1928.

PRESIDENT'S ADDRESS. PROF. O. FOERSTER, Breslau.

Of late, criticism has been directed against the modern tendency toward specialization and the increased dependence on the laboratory for diagnosis. The critics claim that specialization has gone altogether too far; they demand a return to the clinic and the elimination of complicated methods. They desire less analytic dismembering in diagnosis, more intuition, less science and more therapeutic art. In other words, their cry is: a return to general medicine.

Undoubtedly, there is a grain of truth in many of the criticisms, but this does not justify the uprooting of an old established system. It is true that the main object in medicine is to cure the patient, and to try to help him as much as possible, and, therefore, that this should be kept in mind in all investigations and experimental research; but, after all, medicine is a science and the healing art is applied science. In order to be able to cure and to help, one must study medicine as a science and acquire its scientific fundamentals. No other branch in medicine exemplifies this point more than does neurology. How could one take care of a brain tumor without knowing its location and without knowing there was even a question of brain tumor; and how would it be possible to know but for the preceding 100 years of anatomic and physiologic investigations of the brain? One of the advances in neurology is the successful sectioning of the anterolateral columns for the relief of uncontrollable pain. This was made possible only after experimental physiology established the exact location and course of the pain-conducting tract in the cord. The successful operation on the gasserian ganglion for pain in the face and the avoiding of a corneal ulcer depend on the recently gained knowledge of the exact location of the anteromedial fibers in the trigeminus root. The x-rays, the injection of iodized oil, the examination of the spinal fluid and the encephalogram are almost indispensable in differential diagnosis and exact localization in cases of tumor of the cord or brain, and in different types of hydrocephalus.

It is true that fundamentally the study of anatomy, physiology and pathology, was largely theoretical. This was rather fortunate, for the ideas of the true investigator were, thus, not restricted; the results of his labors, therefore, are far-reaching. In 1861, H. Jackson first reported his investigations on the motor centers in the human brain. About the same time came Broca's discovery of the relation between motor aphasia and lesions at the lower third left frontal convolution. These may be considered the beginning of local brain diagnosis. It was not until 1888, however, that Sir Williams Macewen, on the basis of an exact diagnosis, was the first successfully to remove a brain tumor in a man.

Coming more specifically to the question of neurology Foerster called to account those internists who would deny it to be a special branch of medicine claiming this field to be in their domain. How is it possible, at this stage of advancement, for a person to master, in addition to the enormous field of internal medicine, the anatomy, physiology and pathology of the entire nervous system, and also its difficult therapeutic methods? The neurologist himself finds it a task to keep up with rapid advances in the various fields. To be sure, there is a most intimate connection between internal medicine and neurology, but it is an entirely different matter when the internist claims a monopoly of the entire field of neurology, declaring that there is no necessity for the creation of independent clinics in neurology, or for hospital divisions, institutions, teaching facilities and teachers in neurology. There would be some justification in his arguments if he were in a position to master that field and possessed the knowledge and ability required to teach the subject in the way the present advanced knowledge demands. A careful investigation of this question will bring its own answer. [Foerster's criticism can be applied with even greater force to the conditions in the United States.—Abstracter.]

Nor is it enough for the neurologist to master the anatomy, physiology and pathology of the nervous system: he should be well up in diagnostic methods; he should be his own technician and not depend on others for his lumbar puncture, encephalogram, injection of iodized oil and ventricular and suboccipital punctures. He is required to have a knowledge of therapeutics and, if possible, also of the surgical treatment of the central and the peripheral nervous system, including orthopedic repair of ligaments.

On the other hand, neurology must always stand in close association with internal medicine, and especially with some of its branches, such as ophthalmology, otology and dermatology. The neurologist must recognize whether the disease process is *sui generis* or is merely a reflection of a disease process in some other organ or organs. Neuralgia in the arm may often be merely an expression of a myocarditis or an aortitis; headaches may be the result of kidney disturbances or hypertension, etc. In such cases, the neurologist must appeal to the internist. Neurology must, therefore, stand on the foundation of internal medicine.

Similar criticism can be applied, although with less force to the relation between neurology and psychiatry. Nowadays it is most difficult to master both branches, to be productive in both and to keep up with the advances in both branches, although one must keep in mind the close association between neurology and psychiatry. Many nervous diseases depend on a local condition of the brain, but there are a large number that depend on a disease process affecting the entire body, expressing itself either mentally or physically or in both ways. Such cases belong to either the neurologist or the psychiatrist. Strictly speaking, every disease represents a psychophysical problem.

It is often claimed that functional cases belong exclusively to psychiatry. But even those types of cases may show a double picture. Let us not be led into the mistaken belief that, with the establishment of certain bodily symptom-complexes as psychogenic, the matter is entirely settled. The problem is just beginning. It is absolutely essential to discover why in one hysterical patient after a fall, after a stormy emotion or under the influence of a strong wish or desire, a torticollis will develop; in another, a pseudospastic paralysis of a leg; in a third, a particular contracture, and in a fourth gastro-intestinal disturbances. Psychology can explain this but partly, if at all. A most careful analysis of the neurodynamic process is essential. Foerster is of the opinion that careful investigations into the pathophysiology of the basal ganglia may lead to some understanding of functional disturbances. It is often asserted that hysteria has no pathologic anatomy, and cannot have such. There may be none in the sense of an exogenous disease process, but it can earnestly be discussed whether hysteria may not have an anatomy in the sense of a diminution of fibers in certain parts of the nervous system or in a structural abnormality, perhaps only a diminished chemical substance, or perhaps some aberration in the architectonic structure of certain parts of the gray matter.

When Freud teaches that the neurosis is the result of a suppression of an unpleasant experience in the subconsciousness, it is answered that the suppression, psychologically considered, means nothing more than forgetting. One must ask what brought about a splitting of those neurodynamic processes which stand in relation to the content of the experience, and that which represents the correlation of the affect. Why does the former become extinguished and the latter persist to express its activity in the somatic field? It seems imperative that a definite, apparently preformed, abnormality of the nervous system is dealt with. The conception that the neurosis follows the splitting up is untenable; one must rather understand that the splitting is generally the result of a pre-existent abnormality of the nervous system, and that the affective process continues and exerts its influence on the somatic as well as on the psychic fields. Thus, psychoanalytic therapy though useful, can have only a palliative influence.

Interesting observations were made during operations on the human brain. When pressure is applied locally to the medulla a particular psychic syndrome develops, namely, tiredness, numbness and unconsciousness; on the other hand, when pressure is applied to the anterior lower parts of the brain stem, the opposite psychic syndrome appears, intellectual activity, talkativeness and flight of ideas. It is possible, therefore, to bring about two opposite psychic states from two different parts of the brain — in one, elimination of consciousness, and in the other increased mental activity. The conception of personality is not to be separated from the conception of structure. The word structure implies different parts; the conception of parts without a whole is unthinkable, also the conception of the whole without the parts. Analysis and synthesis go hand in hand; this regulates and controls the relation of internal medicine and its separate branches.

I. The Vegetative Nervous System. Dr. W. Braeucker, Hamburg, Germany.

THE ANATOMY AND SURGERY OF THE VEGETATIVE NERVOUS SYSTEM

To the old anatomists and physiologist the conception of the vegetative nervous system was, approximately, what one today considers the sympathetic nervous system. On macroscopic examination, the presence of a large number of ganglionic swellings appeared to them to be a special characteristic of the sympathetic. Winslow compared these ganglia with little brains and considered them as scattered primary stations of the sympathetic. When Bichat first introduced the concept of a contrast, between the animal and the organic (or vegetative) nervous system, he assigned to the vegetative system the regulation of the automatic and instinctive movements, and also the supervision of nutrition and secretion. Bichat considered each ganglion independent; the sum of the sympathetic ganglia he considered to bear a relation to the vegetative system such as the brain and spinal cord bear to the animal system. Thus, the two systems were definitely separated one from the other.

Soon after came the work of Müller and Remak on the peripheral nerves of the two systems. The questions concerning the origin and termination of the nonmyelinated fibers is not settled even now.

There are three important problems:

1. To locate the vegetative fibers in the brain and spinal cord.
2. To determine the conducting tracts between the centers and the periphery.
3. To ascertain the importance which the ganglia have in the vegetative system.

THE VEGETATIVE CENTERS

On the basis of physiologic and pathologic observations, cerebral centers are assumed which are superordinated over the entire vegetative system. They are assumed to be in relation to the afferent sensory tracts as well as the psychic centers, and to send forth efferent fibers to deep-lying centers scattered over the entire brain. So far, it has not been possible to prove them histologically. A vegetative center is assumed in the corpus striatum which too has not been anatomically proved.

Karplus and Kreidl were the first to show that there are vegetative centers in the midbrain. According to Greving, all vegetative centers in the spinal cord and brain stem show a certain similarity in their cell form. Unlike the large multipolar anterior horn cells, the cells of the visceral vagus and of the visceral oculomotor and the lateral horns of the cord are considerably smaller; they are unipolar or bipolar, and seldom have three nerve processes; they have a large nucleus and a small cell body which gradually passes into a relatively long process; the Nissl bodies are irregular and clumped together. They are generally pear-shaped or club-shaped and are usually grouped in definite positions in the nuclei. Greving found many groups of similarly formed cells in the hypothalamus. In the walls of the third ventricle are seen other supposedly vegetative nuclei: (1) the cells of the central gray matter; (2) the oval area of the nucleus paraventricularis; (3) the nucleus interfornicatus, and (4) the nucleus supra-opticus. Two more nuclei, lying more caudad, also considered as vegetative are: the nucleus paramedianus lying in the wall of the third ventricle, and a small nucleus in the corpus mammillare. These nuclei are spoken of as vegetative, on account of their histologic picture, and also because they are phylogenetically very old. Experimental confirmation of this theory has not yet appeared. Greving also investigated the fibrous association between the midbrain and the forebrain and other neighboring parts.

There is more definite knowledge on the nuclei of the brain stem. In the midbrain lies the so-called visceral oculomotor nucleus, which is composed of several cell groups. In the neighborhood of the facial nucleus, there are groups of cells, the fibers of which, passing through the sphenopalatine ganglion, are assumed to innervate the tear glands, the glands of the mucous membrane of the nose and the oral cavities. The dorsal vagus nucleus has been studied most carefully. Gehuchten and Molhandt found that the efferent vegetative vagus fibers come from the dorsal vagus nucleus; they innervate the heart, stomach, small intestine, trachia, bronchia and the lungs, and also send a descending bundle to the cervical sympathetic. More recently Blumenau came to the conclusion that the center for the vagus fibers that go to the heart lies in the dorsal nucleus.

The vegetative centers in the cord were described by Stilling as the lateral horn group, by Clarke as intermediolateral tract and by Waldeyer as lateral horn cells. It was after Gaskell in 1885 expressed the opinion that the lateral horn cells of the cord give rise to the fibers that go to the gangliated cord, that its relation to the peripheral vegetative system was experimentally studied by Anderson, Langley, Bruce and many others. The cells of the vegetative system in the cord are localized between the first thoracic and second lumbar and again between the second and fourth sacral nerves. In the opinion of Bruce, the intermediolateral tract is divisible into three parts. According to Kai the vegetative cells extend through the entire cord. The observations of Poljak, Bertrand, Ivan and Van Boegert and others, point to the fact that aside from the typical lateral horn cells, there are other vegetative elements in the spinal cord. The results of all this work on the centers of the vegetative system as obtained through morphologic studies are not clear. A definite morphologic knowledge of the vegetative centers is yet far distant.

THE STRUCTURE OF THE PERIPHERAL VEGETATIVE NERVOUS SYSTEM

On the basis of Gaskell and Langley's investigation, a peripheral vegetative system which represents the present conception was established. There are three large exits for the vegetative fibers in the cord, including the brain stem: one is cranial, one thoracolumbar and one sacral. They enter two places: where the brachial and lumbosacral plexus leave the cord. All efferent vegetative fibers are fine and myelinated. In the thoracolumbar region, the fibers pass over the anterior roots, and enter either the vertebral ganglion of the gangliated cord or through this into the prevertebral ganglion near the abdominal aorta: from the sympathetic cells of this ganglion arise, then, nonmyelinated fibers which run to the organs, blood vessels and glands. Langley determined the different tracts by injections

of nicotine, which affects the preganglion fibers, but has no influence on the postganglion fibers. This method of investigation led to a confirmation of Gaskell's views regarding the two types of fibers in the sympathetic tracts, between which a motor cell is interpolated. Each vegetative tract is composed of two neurons and the postganglion fibers form the end neurons of the efferent system; they are nonmyelinated and nonafferent. Langley investigated this problem with the degeneration method. After sectioning a ramus communicantes, he could find no degenerated fibers in its central end; therefore the presence of sensory cells in the gangliated cord is excluded. Also after sectioning branches of the gangliated cord, he could find no degenerated fibers in its central part; therefore, the prevertebral ganglion could not contain sensory cells. All afferent fibers come from the spinal ganglion of the posterior root; they have no connection with the sympathetic cells, and they are all myelinated. On the other hand, all nonmyelinated fibers are efferent. The vegetative system is, therefore, not an independent nervous system: it is composed solely of efferent tracts, and it does not possess an individual sensibility, only that which comes from the cerebrospinal system. Since within the vegetative systems the cranial and the sacral parts show different reactions to stimuli and to toxins than does the thoracolumbar part, the first parts are designated as the cranial and sacral parasympathetic system, while the thoracolumbar is called the sympathetic.

These are the essential points according to Langley and Gaskell, and, with slight modifications, they have received general recognition. In recent years, however, a number of observations have been reported which indicate that this teaching is, in some respects, too schematic and cannot be brought in accord with morphologic evidence.

Gaskell's conception that all preganglion fibers are myelinated and the postganglion fibers nonmyelinated was already disproved by Kölliker, Langley and Dogiel, who observed myelinated fibers coming from sympathetic cells. Of late, the reliability of neurologic investigations has considerably increased owing to an improved histologic technic, especially through the work of Stöhr. He has shown that not all fibers coming from the sympathetic cells are nonmyelinated, but that fibers coming from sympathetic cells may become myelinated. Nonmyelinated sympathetic fibers may again become covered with a myelinated sheet, just as cerebrospinal fibers may become nonmyelinated in end-organs. Furthermore, Gaskell and others designated the fine myelinated fibers as preganglionic fibers of the vegetative system, and the fibers with a more marked myelin cover as those belonging to the cerebrospinal system. Stöhr, on the other hand, showed that there are different kinds of myelinated fibers in the gangliated cord: the fibers show here a continuous transition in caliber from the very thick to the finest; to divide them into thick, medium thick and fine fibers is arbitrary. The amount of myelin a nerve fiber possesses never forms a criterion for its point of origin. According to Stöhr, morphology of the nerve fibers does not permit any conclusion as regards function. Harman investigated the rami communicantes in man, from the fourth cervical to the fourth thoracic. Fine myelinated fibers of from 1.8 to 3.6 microns in diameter he considered as efferent sympathetic fibers, and all thicker ones as sensory fibers; and, since he found the finer fibers mainly in the first to fourth thoracic nerves, he designated the first thoracic as the upper exit point boundary of the efferent sympathetic fibers. According to Stöhr, this too is doubtful.

Gaskell was of the opinion that the posterior roots contain only myelinated fibers. But long ago Kölliker, Dogiel and Cajal showed that the spinal ganglion contain nonmyelinated fibers. According to Stöhr, there is no doubt that nonmyelinated fibers are present in the anterior as in the posterior roots, as well as in the spinal ganglion, and that they are connected with the gangliated cord.

Langley and Gaskell's opinion that the sympathetic does not possess its own sensory function cannot be morphologically substantiated. After section of the rami communicantes, or the gangliated cord, or some of its branches, definite tigrolysis was found in the spinal ganglion cells. Likewise after cutting through the posterior roots, or after removing the spinal ganglion, one could observe

degeneration phenomena in the myelinated fibers of the gangliated cord. In the early embryonic state of the sparrow and the pig, Rossi was able to follow the peripheral branches of certain spinal ganglion cells as far as the rami communicantes. From these observations it is concluded that viscerosensory fibers pass from the spinal ganglion into the gangliated cord through the rami communicantes. But it is interpreted rather in accordance with Langley's theory. Stöhr contradicted this. This conception has the fault that it undertakes a morphologic division of the sympathetic when there is no basis for it. The myelinated fibers from the anterior roots going to the sympathetic could, on similar morphologic grounds, be ascribed to the cerebrospinal system. Since it was established with certainty that there are sensory endings in the heart, in the pancreas, in the mesentery and in the bladder, Stöhr saw no morphologic reason to consider those afferent fibers which are connected with the sympathetic area as belonging to any system other than the sympathetic.

Investigations were not lacking in which an attempt was made to establish the cells of origin in the sympathetic plexus of sensory sympathetic fibers. Dogiel differentiated certain types of sympathetic cells as sensory ganglion cells. He also saw a number of nonmyelinated fibers pass from the rami communicates into the spinal ganglion and end in pericellular nets around the cells. Carpenter and Conel could find no sharp line of demarcation between motor and sensory types of cells. Langley, as noted before, was of the opinion that all the sympathetic cells are motor. According to Stöhr, all such classifications are purely arbitrary. In his opinion, all experimental investigation, as regards the course of the fibers in the rami communicantes and the gangliated cord, should be evaluated with care, since only a few investigators so far master the histologic methods as to be able to show degeneration phenomena in myelinated and especially in the complete nonmyelinated elements. Stöhr's conception that the nonmyelinated fibers are functionally the same as the myelinated fibers finds confirmation in the experimental work of Allen, and also of Windle, who found that the pain tracts of the teeth are formed partly of nonmyelinated and poorly myelinated fibers. Morphologically, it is definitely established that the rami communicantes contain myelinated and nonmyelinated fibers which go through the anterior and posterior roots to the gangliated cord. The amount of myelin a fiber possesses is no indication whether it belongs to the sympathetic or the cerebrospinal system. Sensory fibers must also be present in the rami communicantes, since sensory endings are present in the extension area of the sympathetic, and after section of a sympathetic area tigrolytic cells are found in the associated spinal ganglion. So far, no exact clarification has been given in the question of the origin of the different fiber types in the rami communicantes.

Langley's double neuron theory depends on the reaction to nicotine. It is thought that the preganglionic fiber ends around a cell in the sympathetic ganglion and that the postganglionic neuron begins from this cell. All vegetative tracts, accordingly, are composed of two neurons. Many authors describe a number of pericellular endings. Stöhr, however, proved their results faulty and dependent on poor histologic technic. According to Stöhr the sympathetic system is to be conceived of as a closed plasmodium, as a complicated net of a large expansion which in the furthest periphery sends out fine branches in the epithelium, in the glands and in the smooth muscle cells. There is no morphologic basis for Langley's double neuron theory. The reaction to nicotine shows only that the morphologic unit nerve net is not also composed of similar physiologic components. Langley and Gaskell's theory of the structure of the vegetative nervous system is generally accepted; yet there are many contradictions. It appears unlikely that the vegetative centers are limited to the segments as given by the schemata. Furthermore, this theory maintains that the vegetative fibers pass over the anterior roots, that it is composed of fine myelinated fibers, that it ends in motor cells, that all vegetative tracts are composed of two connected neurons, that the postganglionic neuron is nonmyelinated and that sensory fibers are not present, all of which is contrary to the morphologic observations.

THE CRANIAL PORTION OF THE VEGETATIVE SYSTEM IN MAN

By the term "Sympathetic nervous System" Braeucker does not understand what is usually taught in the hypothetic schemata; his conception is morphologic; under the peripheral sympathetic he includes the gangliated cord, all its rami communicantes and its peripheral branches. He believes that the physiologic conception of "parasympathetic" can be dispensed with.

[The author here showed a number of drawings from carefully prepared preparations.] Behind and medial to the internal carotid, at a point where the common carotid divides, near the three upper cervical nerves lies the spindle-shaped superior cervical ganglion. This has connections with the upper cervical nerves, and with the glossopharyngeus, vagus and hypoglossus. The function of the connecting branch has not yet been made clear. It is not altogether improbable that these connecting branches represent roots as well as peripheral branches of the sympathetic.

Of the peripheral branches of the upper cervical ganglion the author mentions only the rami laryngopharyngei, which, with the corresponding branches of the glossopharyngeus and the vagus, form the plexus pharyngeus and, in addition, the external carotid nerves. They appear here in many branches. Some branches go to the external carotid and some also to the internal carotid. Some branches go to the blood vessels from the glossopharyngeus, vagus and hypoglossus and its descending ramus. The coalition of all these branches at the dividing point of the carotid, forms a rolled up net, in which smaller ganglia are present and from which again secondary perivascular nets with individual branches go to the periphery. Thus, each blood vessel possesses a perivascular nerve net, which, without a break, extends to the periphery, and during its course constantly receives small additions from the regional nerves. The formation of the perivascular nerve net differs in each blood vessel. But the principle of net or plexus formation is the same in all blood vessels of the head and the whole body. It can be put down as a general law.

The cranial continuation of the upper cervical ganglion is the internal carotid nerve. It passes behind the internal carotid and divides into a more pronounced lateral, and a finer medial twig. While the lateral twig passes on the posterior lateral, the medial passes on the inner lower side of the carotid. Here with their branches, they form the plexus caroticus internus from which arise connecting branches to other nerves. The nervus caroticotympanicus inferior, the nervus caroticotympanicus superior and the nervus petrosus profundus minor enter fine bony canals and pass through the anterior wall of the tympanic cavity to unite at the lower border of the promontorium with the nervus tympanicus. The first is said to carry fibers of the glossopharyngeus to the carotid plexus and the latter sympathetic fibers to the tympanic nerve.

The foramen lacerum is filled up with a thick fibrous mass. Here the lateral twig gives up a stout gray branch, which passes through the fibrous mass as the nervus petrosus profundus, unites with the nervus petrosus superficialis major and enters the vidian canal as the vidian nerve. The vidian nerve enters the posterior point of the sphenopalatine ganglion. The nervus petrosus profundus is considered as the cranial continuation of the gangliated cord. The plexus caroticus has also several fine connecting fibers with the nervus petrosus superficialis major. Arnold was able to follow a branch of this nerve up to the geniculate ganglion; in this way a connection should exist between the facial nerve and the carotid plexus.

On the anterior surface of the petrous portion of the temporal bone and over the foramen lacerum, partly lying on the lateral wall of the sinus cavernosus is found the semilunar (gasserian) ganglion. It is surrounded by a duplication of the dura which causes difficulty in making fine preparations of this area. It is necessary to work under water and with a low power magnification in the microscopic examination of each nerve with its connecting fibers. The gasserian ganglion was cut squarely across at the carotid, and the under surface was carefully laid free. The author was able to show some nerve fibers coming from

the under surface of the ganglion, to enter the carotid plexus. The abducens crosses the carotid and forms several connections with the carotid plexus. Another branch of the abducens passes upward in that part of the plexus caroticus which surround the fourth and fifth arches of the carotid, and is designated as the plexus cavernosus. Also branches from the ophthalmicus, from the trochlearis and from the oculomotorius enter the plexus cavernosus. Therefore the cranial portion of the sympathetic is connected with nearly all the cranial nerves.

The question remains unsettled whether these connecting branches should be considered as sympathetic roots or as peripheral branches which supply sympathetic fibers to the cranial nerves. Physiology teaches that sympathetic fibers to the cranial nerves are transmitted through these connections. Morphologically, this has not been established.

The extension of the plexus cavernosus passes on with the carotid also to its end-branches. The ophthalmic artery receives in the orbital cavity additional branches from the regional nerves. It appears also that the cerebral branches of the carotid artery receive sympathetic nerves. Occasional observations lead the author to consider it probable that the cerebral arteries are also supplied by direct fibers from the brain substance.

A few more ganglia belong to the cranial sympathetic. The ciliary ganglion lies on the outer side of the opticus. It is connected through a short thick radix with the lower branch of the oculomotor nerve, through a long thin radix with the nervus nasociliaris and through a sympathetic radix with the plexus cavernosus. The first radix is considered to be motor; the second, sensory, and the third, sympathetic.

In the pterygopalatine fossa lies the sphenopalatine ganglion. The sphenopalatine nerve is considered to be a sensory radix; the nervus petrosus superficialis major, a motor radix, and the nervus petrosus profundus, a sympathetic radix. The branches of the ganglion go as the rami nasalis posteriores to the nasal cavity, as nervi palatini to the oral cavity and as rami orbitales to the orbital cavity.

The ganglion oticum lies right under the foramen ovale, on the medial side of the mandibular nerve and the lateral surface of the tensor veli muscle. The ganglion receives a few small branches from the mandibularis which Arnold considered a motor radix. The latter forms a connection between the ganglion and the facial nerve and the glossopharyngeus.

The submaxillary ganglion lies over the submaxillary gland. Here it is embedded in the lingual nerve. A macroscopic difference between a motor and sensory radix is impossible. Arnold considered as sympathetic a few fibers running from the external maxillary to the ganglion. These fibers could, with equal justice, be considered ganglion branches going to the perivascular net. Branches from the ganglion and from the lingual also go to the sublingual gland.

At present it is not possible to make a differentiation in the sympathetic ganglion between motor, sensory and sympathetic radixes. It is, therefore, of importance to know the morphologic relations between the entering nerve branches, the ganglion and its cells. In anatomy one is concerned with structural relations. When one compares the structural relations of the vegetative elements, of the oculomotor and the vagus with the sympathetic, no morphologic difference can be noted in its cells of origin its central organs, its peripheral fibers or its peripheral ganglion. Hence, anatomically there is no basis to speak of parasympathetic, and one designates simply as vegetative the elements present in the cerebrospinal nerves.

Some authors consider the cranial sympathetic ganglion partly sympathetic and partly cerebrospinal. They support their views on the basis of the different types of cells found in the ganglia. These assertions, however, are contradictory. L. R. Müller stated that the cranial ganglia in man contain only multipolar cells, and this conception is largely accepted today. Different types of preganglionic fiber endings around the ganglion cells have been described, but nothing definite is known as to what part is played by the vegetative tracts of the different cranial nerves in the construction of the sympathetic cranial ganglia.

Another word concerning Langley's dual neuron theory: Apolant, after sectioning the oculomotorius at its point of exit, found only the fibers up to the ciliary ganglion to degenerate; the ganglion itself remained intact and, likewise, the short ciliary nerves.

According to von Lenhossék, the neurites of the nerve cells in the sphenopalatine ganglion go to the mucous membrane of the nose and the palate where they end freely. Yagita, after cutting through the nervus petrosus superficialis major saw that the fibers degenerate only up to the sphenopalatine ganglion. The postganglionic fibers are said to be distributed to the mucous membrane of the nose and the palate. If this were true, then one should expect to find an atrophy in the corresponding mucous membrane after extirpation of the sphenopalatine ganglion. But this is not observed. Braeucker performed this operation on several patients, and he found that the mucous membrane of the nose and palate remained intact. Hence, not all peripheral innervation is lost after sectioning and degeneration of the postganglionic fibers.

The relation of the cranial ganglia among themselves is complex and variable. In one case the author found a fiber going from the rami orbitalis to the lower twig of the oculomotor nerve. Tiedemann and Arnold described such a branch to the ciliary ganglion. Others saw such fibers going to the opticus. Arnold also saw association branches to the plexus cavernosus. Meckel, Bock, Valentin and Faesebeck described association branches with the abducens. In one case Rousset found one fiber going to the abducens, one to the trochlearis and one to the gasserian ganglion. If the sphenopalatine ganglion in man is touched, pain develops in the upper jaw and radiates to the eye, the ear and at times, also, the angle of the mouth. The same pain will appear under similar conditions after total extirpation of the gasserian ganglion with its three branches. Some connection in the cranial ganglion must, therefore, remain, even after degeneration of the entire peripheral trigeminus. After extirpation of the sphenopalatine ganglion, the author was unable to produce this pain from the pterygopalatine fossa.

The observation that stimulation of the cervical sympathetic affects an organ through different routes suggests that the stimulus enters a nerve net and spreads to several tracts. The two-neuron theory does not hold true for the ciliary and the sphenopalatine ganglia; the individual cranial ganglia are connected among themselves, without the intervention of the trigeminal fibers. These observations substantiate Stöhr's theory that the vegetative system, in form, is a large diffuse net. Macroscopic anatomy cannot furnish further evidence in favor of this theory; moreover, the vegetative elements cannot be separated from the cerebrospinal elements. Especially noteworthy is the fact that branches from all cranial nerves go to the blood vessels. Ganglion cells were also found in all cranial nerves, the significance of which fact is not yet clear. At present we have an incomplete picture of the extension of the vegetative nervous system in its cranial division. The cranial part of the vegetative system is a part of the peripheral nervous systems, and it extends over the nerve nets of the carotids, vetebrals and all cranial nerves.

THE SURGICAL IMPORTANCE OF THE CRANIAL DIVISION OF THE VEGETATIVE SYSTEMS: MIGRAINE

Several types of operations were proposed for the relief of migraine. Starting with the conception that the individual attacks depend on a spasm of the cranial blood vessels, and that these blood vessels are innervated by the cervical sympathetic, operations were performed on the one hand on the cervical sympathetic and on the other, on the perivascular nerve plexus of the internal and common carotid. Jonnesco resected the entire cervical sympathetic and reported good results. Witzel reported good results with periarterial sympathectomy on the carotid. The author operated on a man, who had suffered for twenty-five years from attacks of severe ophthalmoplegic migraine. He laid open the entire upper end of the upper cervical ganglion and, without doubt, sectioned the internal carotid nerve and the fibers ascending with the artery. The result was entirely negative. The

attacks came on as before the operation, including vasomotor disturbances (a functional disturbance was carefully ruled out). Amyl nitrite relieved the pain for a minute. Hence, the blood vessels of the brain must have another innervation besides the cervical sympathetic.

Sluder and Frazier reported that pain due to migraine is relieved by injections into the sphenopalatine ganglion. Braeucker only once found slight relief from such an injection of procaine hydrochloride; in two other cases it had no influence. The sphenopalatine ganglion, therefore, can have no important relation to the pain. Richter came to the conclusion that attacks of migraine may depend on spasm of the vertebral artery to which Foerster agreed. Twice during an attack, Braeucker blocked the vertebral nerves of the inferior cervical ganglion, without any result. He then investigated all the cranial nerves. When the needle pierced the gasserian ganglion, the pain appeared and the patient cried out, "this is the real pain and such as I have never had before." An injection of 0.5 cc. of alcohol developed an incomplete anesthesia and an attack which lasted eight days. Instead of affording relief it apparently caused an irritation of the trigeminus. When the same place was pierced again severe pain developed once more. Slow injections of 1.5 cc. induced complete anesthesia and the pain stopped. Later milder attacks occurred without the former associated symptoms, such as vomiting and vasomotor disturbances. The patient himself had the feeling that the nerve responsible for the attacks was partly under control. In two other mild cases of migraine the attacks were cut short by injection in the gasserian ganglion. The author again calls attention to the fact that the oculomotor, the trochlear, the abducens and especially the trigeminus are connected with the internal carotid through nerve branches. It is possible (especially in cases of ophthalmoplegic migraine) that the pain depends on a pathologic process in the trigeminal nucleus, the radiation of this process to the periphery over vascular nerve branches developing an abnormal vasomotor condition in the region of the internal carotid, which brings on the attack.

REMARKS ON TRIGEMINUS NEURALGIA

When medical, x-ray, injection and other treatments fail, and surgical measures are decided on, section of the retroganglion root becomes the method of choice. Section of the cervical sympathetic has given only temporary relief. But Pette showed a close relationship between neuralgia and the sympathetic system. Kulenkampff was of the opinion that the vasomotor and secretory manifestations in trigeminal neuralgia are indications of sympathetic disturbance. He believed that the attacks are brought on by a spasm of the blood vessels supplying the gasserian ganglion, and he advised a periarterial sympathectomy on the internal carotid. No permanent relief can be expected from this procedure, however, even though the vasomotor theory is true, for the arteries of the gasserian ganglion come from the internal carotid, and they receive their nerve supply largely from the gasserian ganglion itself — partly, also, from the carotid or cavernous plexus. Hence, the sympathetic center which produces the vasomotor symptoms has its seat not in the cervical sympathetic but in the gasserian ganglion itself which possesses multipolar cells and sends branches to the blood vessels. Pette reported several cases in which trigeminal neuralgia developed after extirpation of the cervical ganglion. This can be explained by the fact that after a vegetative nerve is sectioned an increased irritability develops in the distal part. The cranial vegetative system represents a diffused network in which lie several ganglionic centers. After extirpation of the superior cervical ganglion, the neighboring centers fall into an increased irritability and the overstimulated vegetative centers in the gasserian ganglion condition a trigeminal neuralgia. Increased irritability in the ciliary ganglion can also cause pain in the eye. All vegetative centers of the body may become overirritated with sensory disturbance over the entire corresponding part. But this condition of altered irritability gradually subsides. When an intermittent trigeminal neuralgia can be favorably influenced by resection of the cervical sympathetic, and when the same procedure may bring on a trigeminal neuralgia, there is probably an alternating relation between the function of the vegetative and the

sensory ganglion cells. The fact that an operation on the sympathetic nerve does not cure the neuralgia and that section of the trigeminus does seems to indicate that the neuralgia develops in the sensory elements of the ganglion and that the vasomotor and secretory manifestations are the results of this pathologic process, and not its cause.

CONCERNING PSEUDOTRIGEMINAL NEURALGIA

The author described the case of a woman, aged 24, who for eight years suffered from pain in the upper teeth on the left side. Periodontitis was present at the time. The pain remained even after all the teeth were extracted and after five operations on the jaw. Injections of alcohol, first in the maxillaris and later in the gasserian ganglion greatly increased the pain. The pain was continuous, varying in intensity, was felt more in the depth of the left upper jaw and radiated from here to the root of the nose, the eye, the orbital edges, the angle of the mouth, the ear, the temple and, at times, the back of the head; when the pain was unusually sharp it spread to the top of the head, the neck, the shoulder, the arm, the chest and, at times, the other side of the head. There was a constant dull pain in the upper jaw; at times it assumed a burning, boring character. Eating and talking did not bring on attacks. The failure to respond to injections of alcohol indicated that this was not a true case of trigeminal neuralgia. The picture was more like a neuralgia of the sphenopalatine ganglion as described by Sluder. After psychotherapy failed, an injection of procaine hydrochloride was made into the sphenopalatine ganglion. The pain ceased in the jaw, in the root of the nose and in the angle of the mouth, but was even increased in the eye, ear and temple. When the needle touched the gasserian ganglion, however, the patient cried out, "This is the place the pain comes from." An injection of alcohol produced incomplete anesthesia. The conclusion was, therefore, that Sluder's neuralgia was complicated by a chronic irritation in the gasserian ganglion after an injection of alcohol. The gasserian ganglion with the three branches was extirpated. The operation produced a total anesthesia for light touch in the trigeminal area. Deep sensibility was greatly increased. Pressure over the upper jaw was painful. Subjectively there was some improvement, but the pain in the upper jaw and in its radiating areas remained.

Sluder considered this pain to be caused by a diseased condition of the sphenopalatine ganglion. When this ganglion was touched with a needle there developed increased pain in the upper jaw and wavelike pains that spread to the eye, ear, temple, angle of the mouth and, at times, back of the head. Injections of procaine hydrochloride relieved the pain in the jaw; in the other places the effect was not constant. One might conceive that a pathologic process was present in the sphenopalatine ganglion which, by radiation, implicated the neighboring vegetative system. The ganglion with all its roots and branches was, therefore, removed. Soon after the operation the pain was even worse than before; later it subsided, but the pain in the eye, ear and angle of the mouth remained. Twitching and pain spread over the entire half the face, and when the pain was severe it also involved the upper jaw as before. Deep sensibility was increased. Practically, the removal of the sphenopalatine ganglion did not accomplish any more than the removal of the gasserian ganglion. Cushing described such a case. He first removed the gasserian and later the sphenopalatine ganglion. The pain remained the same, and there was no change thirteen years later. Cushing remarked that in those cases one could speak of "central pain or pseudoneuralgia, psychalgia or hysteria." But this is not satisfactory. One must rather look for some other source to account for the pain. How can the condition be explained in the foregoing case? With the ganglionectomy the trigeminal elements are eliminated; with the operation on the sphenopalatine ganglion are interrupted the nerves to the orbital cavity, the facial nerve, the internal carotid plexus and the otic ganglion; the perivascular web of the maxillaris cannot come into question, since the end part of the blood vessel was removed. All afferent tracts of the upper jaw apparently were sectioned. Can there be still another nerve connection?

The author made several injections in a case of neuralgia of the cervical nerves. Touching of the first cervical nerve caused pain and parasthesia in the forehead; of the second cervical, pain in the temple; of the third cervical, pain in the ear and forehead, and of the fourth cervical, pain in the upper jaw and nose. The involved areas were not always the same size. Injections of procaine hydrochloride in these nerves often controlled the pain for several days. The author therefore sectioned from the first to the fourth cervical nerves together with the rami of the external carotid, which come largely from the upper cervical ganglion and the hypoglossus. The operation relieved the increased deep sensibility in the trigeminal area; the upper jaw also was no longer sensitive to pressure. The pain in the upper jaw and its radiation over the face, head, neck and shoulder also disappeared, and the patient was cured.

The external maxillary artery supplies the outer soft parts of the superior maxillary and also sends a branch to the bony part, which anastomoses in the bony wall with branches of the infra-orbital artery. In this way anastomosis also takes place between the perivascular nerve nets of the external maxillary and the plexus dentalis superior, which lies in the superior maxillary wall. This plexus probably contains vegetative elements which do not degenerate after the extirpation of the gasserian and sphenopalatine ganglia. Apparently this plexus was the seat of a pathologic process developed from an abscessed condition of the teeth, and this process, localized in the nerve mesh, called forth the entire picture with its symptom-complex. Hence, the pain is transmitted, over the trigeminal tract, over the sphenopalatine ganglion, also over the external submaxillary plexus which transmits centrally the rami of the external and common carotid and the four upper cervical nerves. After the first two tracts are eliminated, the third is still capable of producing the painful condition. It is to be noted that the third branch is not always involved.

The so-called Sluder's neuralgia, therefore, represents a disease of the most peripheral nerves of the superior maxillary region and the pain developed reaches the central organs through the trigeminal and the sympathetic tracts.

THE NECK AND THORACIC PART OF THE VEGETATIVE SYSTEM

[The author presented a carefully prepared specimen of the neck and chest, the gangliated cord lying on the parietal pleura.] The anatomy was described.

According to physiology, all cervical rami communicantes are gray rami—hence, peripheral branches that carry sympathetic fibers to the spinal nerves. If this is correct, the peripheral branches of the superior cervical ganglion, for example the fibers of the upper nerves for the heart, must take the following course: ascending from the thoracic gangliated cord up to the superior cervical ganglion, and from there again descending over the cardiac nerves to the heart. Such a fiber course is most unlikely. Macroscopic observations make it probable that the peripheral branches of the superior cervical ganglion, and also the upper cardiac nerves, come from the rami communicantes with the upper cervical nerves.

THE THYROID INNERVATION

The cervical sympathetic and the upper cardiac nerves pass down over the posterior surface of the gland and there give off to the thyroid many branches, especially the cardiac nerves. Also the middle and the lower cardiac nerves or the corresponding cervical ganglion take part in the innervation of the gland. Branches from the superior laryngeus, from the vagus stem and from the recurrens reach the thyroid. All these branches form a plexus, the so-called capsular plexus, which embraces the entire gland. From this plexus go branches to the epithelial bodies. In this capsular net, there is no possibility of differentiating sympathetic from vagus fibers. This holds true for all other organs that receive, at the same time, fibers from the sympathetic and the vagus, or any other cerebrospinal nerves. The fibers of the different nerves enter the individual organs after forming a net, or plexus, in which in the end-distribution, the fibers of the sympathetic origin cannot be isolated from the fibers of any other origin. The author designates this

plexus as a "local organ plexus." In many organs (heart, trachia, bronchia, gastro-intestinal tract, bladder, etc.), there are embedded ganglia in the local organ net, the cells of which show the same structure as the cells of the gangliated cord. The morphologic characteristic consists in nerve nets connected with the central organ by branches from different nerves.

Exophthalmic goiter is generally considered a disease of the thyroid, and many are of the opinion that this disease is caused by a disorder of definite parts of the vegetative system. Attempts were made to effect cure by resection of the cervical sympathetic. According to Reinhard, there are secretory fibers in the cervical sympathetic for the thyroid. Asher and Flack were able to show secretory fibers in the larger nerves. According to Flatow and Schilf, all secretory fibers appear to come from the sympathetic. When one desires to remove in man all the thyroid secretory fibers, one must cut through the sympathetic as well as the vagus fibers. But this is not possible, without sacrificing the laryngeal nerves. Besides, one must consider the capsular net, entire removal of which will endanger the epithelial bodies as well as the recurrens, and technically the procedure is difficult.

The rami mediastinales and the cardiac nerves were next described.

The author was able to show that fibers, from the rami mediastinales of the five upper thoracic segments go regularly to the arch of the aorta and to the cardiac plexus. The fibers from the sympathetic to the cardiac plexus come from the upper cervical ganglion up to the fifth thoracic ganglion. The presence of the newly described thoracic cardiac nerves was substantiated by Cannon, Lewis and Britton, who were able to show that the thoracic cardiac nerves of the sympathetic are present in the cat and that they carry accelerator fibers. Jonnesco and Jonescu found a good functioning heart in patients in whom the superior, middle and inferior cardiac nerves were removed by cutting the sympathetics on both sides, and they concluded that the accelerator nerves are not essential to life. This conclusion is not correct: the sympathectomized patients still have their thoracic cardiac nerves, which are capable of regulating cardiac activity. It is impossible to differentiate sympathetic from vagus fibers in the cardiac plexus, and is entirely arbitrary to assume that only vagus and not sympathetic fibers end in the ganglion of Wrisberg. The net of the aortic arch cannot be separated from the cardiac plexus; there is no boundary line between them. The local plexus of the heart is, therefore, a large plexus which is spread over the aortic arch and the cardium and is connected on all sides with the nets of the neighboring organs.

ANGINA PECTORIS

These anatomic relations offer a definite orientation in the question of the surgical treatment of angina pectoris. Some are of the opinion that the depressor is the sensory nerve of the aorta. According to Jonnesco, there is present in man an isolated depressor. The innervation is too complicated, however, to permit such a one-sided view. It has been definitely established that there are sensory fibers in all branches of the vagus in the neck and in the thorax. Sensory fibers have also been shown to be present in the sympathetic cardiac nerves, and even a depressor function was shown in two of these nerves, the upper and the middle; therefore, the vagus cardiac nerves as well as the sympathetic cardiac nerves contain sensory fibers. Accordingly, when one desires to section all afferent tracts to the heart and aorta a gigantic operation will be required. Moreover, if all the sensory tracts in the peripheral course of the cardiac nerves are sectioned, all the motor tracts to the heart will be destroyed. One might approach the ideal in cutting the sensory fibers and sparing the motor, if that part of the cardiac plexus was cut from which the plexus for the coronary arteries comes. That would be a difficult and dangerous procedure. Since one must not cut all the afferent cardio-aortic tracts, the attack must be made on one of its parts; and since in this entire system of the cardiac plexus the sympathetic elements are in preponderance over the vagus fibers, and since the sympathetic tracts are primarily pain transmitting, the best results are obtained if the attack is made on the sympathetic tracts. Also here one must not cut all segments from the first cervical to the fifth thoracic. The clinical picture must regulate the degree of the operation, and one must attack

only those segments which are the seat of pain. The paravertebral injection of the rami communicantes or of the spinal nerve roots does not give definite information as to which segment is involved. Since the injection of procaine hydrochloride in two or three segments often controls the pain the pathologic process is apparently not as extensive as the clinical picture would indicate. A procaine hydrochloride block often controls the pain for a long time, and should be tried before surgical intervention.

When surgical measures are indicated, the portion to section is either the rami communicantes or the corresponding posterior roots. Hard and fast rules cannot be set down. For section of the posterior root speaks the fact that with preservation of the anterior roots most of the cardiac motor fibers are spared. On the other hand, Foerster's experience speaks against this choice, since he found after sectioning the posterior roots, that the anterior root, as an auxilliary tract, may transmit the pain. This danger is avoided when the corresponding rami communicantes are cut; yet by this method motor fibers are also cut together with the sensory. There is, therefore, no ideal surgical procedure. Perhaps it is best to individualize the choice of operation. In a case in which the heart is weak, sectioning of the posterior roots is, perhaps, to be preferred, as the motor fibers may be spared. In cases in which the heart is in good condition, it is better, perhaps, to cut the rami communicantes. In many cases it will suffice to cut the rami from the fifth cervical to the first thoracic. This procedure still leaves a number of sensory and motor tracts. The radiating pain in the arm is definitely controlled, and it may favorably influence the pain in higher and lower segments without its rami being cut. The results are not altogether satisfactory. In most cases of angina pectoris, however, the sectioning of the rami communicantes from the fifth cervical to the first thoracic is the operation of choice.

THE SYMPATHETIC TRACTS TO THE EXTREMITIES

To the extremities go sweat, secretory, pilomotor and vasomotor tracts. Langley carefully described the course of the sweat secretory fibers in the cat, and lately the author established the same in man. In a patient with hyperhidrosis of the hands and feet, he was able to show that the secretory dermatome goes together with the sensory dermatome, and after section of the rami communicantes the sweating disappeared. The sweat fibers for the upper extremity originate in the fourth to the ninth thoracic segments and reach the gangliated cord over the rami communicantes where they ascend to the first thoracic and inferior cervical ganglion: From there they pass over the rami communicantes into the roots of the brachial plexus, and pass on to the periphery together with the sensory fibers. According to Langley, a switching takes place in the stellate ganglion from the preganglionic to the postganglionic fibers, and he was of the opinion that when the postganglionic fibers are cut there will be a degeneration of the entire postganglionic tract up to the last ending in the sweat gland. In the foregoing case the author cut the rami communicantes for the palm of the hand: The abnormal sweating ceased, and centrally produced heat caused no sweating in the excluded dermatomes; on the administration of pilocarpine, however, some sweating was noted. This indicates that there probably remained in the periphery a part of the sweat tract, through which pilocarpine may have influenced the sweat activity. Stöhr made a histologic study of the skin taken from this patient's hands (both the one on which operation was performed and the other). He could find no difference in the cutaneous nerve nets; no degeneration was found in the skin from the hand operated on. Cutting of the rami communicantes must cause degeneration some place. There must, therefore, be other central places, morphologically not known, which are capable of maintaining the cutaneous nerve nets.

The vasomotor tracts of the upper extremities have, at the beginning, the same course as the secretory tracts and reach the first thoracic and the inferior cervical ganglia. A row of fine branches go from the ganglion to the subclavian artery and vein, and wrap around the vessels, forming a large irregular nerve

plexus, and proceeding in their course with the blood vessels. But the largest mass of the vasomotor fibers pass over the rami communicantes into the roots of the brachial plexus and run with it distally. From the spinal nerves small branches pass to the blood vessels which enter the perivascular nerve plexus, increase and renew it, and carry this net formation to the periphery. At the subclavian artery is thus formed a continuous nerve plexus which extends over the vascular structure with all its branches, up to the finger. The perivascular nerve plexus at the inferior cervical ganglion is formed from direct branches of the sympathetic, but the entire nerve plexus of the peripheral vascular structure is formed from indirect branches, from the sympathetic over the rami communicantes and the spinal nerves. The vasomotor fibers therefore enter the perivascular nerve net through two routes: (1) direct, from the sympathetic; (2) indirect, from the sympathetic over the rami communicantes and the spinal nerves—the direct sympathetic branches form the perivascular net in the neighborhood of the sympathetic, and the indirect in all peripheral vascular areas, and the resulting plexus of both is continuous.

The perivascular nerve net is a special apparatus which may live and function independent of the centers. Foerster reported a case of traumatic section of the brachial plexus distal to the rami communicantes. According to Langley, in the sectioned spinal nerve a degeneration of the spinal and vasomotor elements should have developed, and the nerve plexus of the peripheral vascular structure should have died off. When Foerster stimulated the spinal nerves of the anesthetic area no pain developed, but when he stimulated the digital artery there was severe pain. The nerve plexus of the distal vascular parts was not degenerated although it was cut from its center, and there was present an afferent tract in the perivascular net. The vascular net, therefore, remains intact after section of the rami communicantes. This observation indicates that Langley's conception of a double neuron vasomotor transmission is not correct.

The significance of the perivascular nerve net to the blood vessels is the same as that of the cutaneous nerve net to the skin. A characteristic of the perivascular nerve net is that it represents a local organ net and again a transmission tract. Foerster showed that it possesses an afferent tract. Since the net is formed of vasomotor fibers one must assume also that it possesses an efferent tract. Langley and Schilf spoke against such an efferent tract in its perivascular net. But the fact must be considered that one is concerned with delicate reactions in a complicated net formation, which cannot be tested with coarse experimental stimuli. Observations in human pathology would indicate (although experimental evidence is against it) that the perivascular net must possess also an efferent tract, perhaps only under special pathologic conditions. So far, this assumption is hypothetic. It would seem that normally the vasomotor impulses run over the rami communicantes and the spinal nerves, that is, the main tract; when this main tract is interrupted, it is possible that the auxiliary tract enters gradually as a substitute and may also transmit vasomotor impulses.

Raynaud's disease is said to depend on a pathologic stimulating condition of the sympathetic, which radiates to the hand and the feet and develops circulatory disturbance. The aim of surgical treatment of the disease is to interrupt the vasomotor tract and thereby make ineffective the stimulating condition in the periphery. This result was at first believed by Leriche to be obtainable by partial sympathectomy, but it is evident that partial sympathectomy interrupts only the auxiliary vasomotor tract, the main tract remaining intact. The author has had many experiences in which operation proved unsuccessful, especially in the severe cases; hence, he now resects the entire cervical sympathetic in Raynaud's disease of the hand.

When the rami communicantes of the seventh and second cervical and the sixth thoracic are carefully cut, all the symptoms disappear suddenly. The result is so striking, in fact, that one could assume that Raynaud's disease depends on a central irritation which can be interrupted by section of the transmitting tract after which the symptoms will not return. After several months, however, the

old symptoms may again appear; they are not as severe as they were before, yet they do return. This takes place apparently through the perivascular nerve plexus: The auxiliary tract has taken over the transmission to the periphery. From these experiences it may be concluded that in Raynaud's disease it is not enough to section the corresponding rami communicantes; it is also necessary to interrupt the peripheral perivascular nerve plexus. With the sectioning of the main and the auxiliary tract, the interruption of the vasomotor tract will be complete.

Even with the interruption of both tracts, however, the symptoms may return. This fact is of great theoretical interest. In the case of hyperhidrosis reported here, interruption of the transmission tract brought fairly good results; on the other hand, in Raynaud's disease it is partly successful. This difference in the effects of one and the same operative principle can only be that in each disease there is a different underlying pathologic change. Hyperhidrosis depends on a central, presumably local, pathologic process in the cord. Opinions differ concerning the pathology of Raynaud's disease. The best founded opinion is that of Cassirer. According to him, the disease depends on a disturbance in the entire efferent vasomotor transmission tract, perhaps with greater participation of the vasomotor centers in the cord. To the vasomotor tract also belongs (according to the authors) the perivascular nerve net, which does not degenerate after section of its central connections. This nerve net shows an independence of function, and an increased, pathologically modified susceptibility to stimuli through the blood. In this way the reappearance of the symptoms can be explained, although the transmission tracts were interrupted. The author's experience led him to substantiate Cassirer's opinion concerning the pathologic changes in Raynaud's disease.

This fact does not argue against operation in Raynaud's disease. In cases of a return of symptoms the author suggests a simple method of treatment. It consists in a kind of a dry cupping over the extremities up to the elbows or the knees. This suction brings the blood to the extremity, which swells and fills up with blood. The underlying pathophysiologic mechanism in Raynaud's disease consists in abnormal vascular reflexes bringing disorder to the circulation. This treatment dilates the blood vessels, spasms and abnormal reflexes are overcome, and the influence of a diseased innervation process is controlled through a passive and long maintained stretching of the vascular walls. Such training of the vascular walls maintained over a long period, several hours a day, is capable of overcoming the abnormal nervous process in the perivascular nerve plexus. It does not control the cause of the disease, but its effect is beneficial. This method of treatment controls the disturbances in the side on which the operation is performed much more quickly than it does on the other side. The interruption of the transmission tract is, therefore, to be looked on as essential, even though it cannot make the pathologic process harmless in the entire tract.

The persistence of the perivascular nerve net, after interruption of the transmission tract may lead to the gravest consequences. Gangrene may develop and amputation be found necessary. In cases in which there are large ulcers, it is not enough to section the main vasomotor tract. Such cases demand further procedures. The operative principle of interrupting the transmission tract to the extremities will result in complete success in all cases in which the disease is localized in the vegetative centers or in the central parts of the transmission tract. If the disease also involves the periphery of the transmission tract, the persistence of the sympathetic and plexus will not permit a complete recovery.

The author then described the vagus and sympathetic in the chest cavity. The vagus appears as a nerve root, which, with the main bulk of its vegetative fibers, springs from the dorsal vagus nucleus. During its peripheral course in the neck and in many places in the chest cavity it receives new spinal tributaries over the sympathetic. When the sympathetic branches enter the chest organs independently they unite sooner or later with vagus branches, and in the local organ plexus the former can no longer be isolated from the latter. Vagus and

sympathetic branches form, thus, a large net like diffused fiber system that guarantees the supply of the organ from several segments.

BRONCHIAL ASTHMA

Several years ago, when Kümmell, Sr., reported that by cutting the cervical sympathetic he cured several patients with asthma, the objection was raised that the vagus is a bronchial contracting nerve and the sympathetic a bronchial dilating nerve. A discussion arose as to whether the vagus or the sympathetic should be resected. At that time the author had shown through experiments on animals that the vagus ordinarily brings about a contraction of the bronchi, but at times a dilatation, and in a few cases it was possible to obtain from the corresponding sympathetic a contracting or dilating effect. The sympathetic effect on the bronchi was, indeed, more rare and weaker, yet withal similar to the vagus effect. It was especially striking that one and the same transmission tract should be able to effect contraction and dilatation of the bronchi. Was it, possibly, that the vagus and sympathetic were together in the same tract? The author, in association with Kümmell, Jr., stimulated the vagus root bundle intracranially, in order to obtain an absolutely pure vagus effect. They obtained contractions mainly, but at times also dilatation of the bronchi. They came to the conclusion that the alternating result on stimulation is to be referred to different reactions in the ganglion in the bronchial wall.

Since the bronchomotor fibers of the sympathetic in its totality come together with the vagus fibers first in the region of the plexus pulmonales posterior, it follows that to be certain of sectioning all bronchomotor fibers, one must cut the rami bronchiales posterior. So far, this operation has been performed on five patients. In one of them, on one side, the ramus bronchiales anteriores also was removed. The effect of the operation was carefully observed over several years: The typical severe attacks no longer occurred, and breathing was essentially improved, but when asthmatic conditions arose the symptoms returned. Asthmatic noises were heard over the lung operated on, at times mild, and at times the same as were heard on the other side. Therefore the lung operated on may be affected by a spasm. Pilocarpine will cause a severe cramp in the lung operated on. Since the ganglia in the bronchial wall with all the processes are preserved, the toxin apparently affects the nerve elements that remain. A bronchial spasm may be brought on by psychic emotions; energetic psychotherapy and breathing exercise may bring about a cure. In addition, this spasm could not come on by way of the nerve tract, but it takes place apparently by the way of the blood stream, through the intervention of a hormonal influence. The interruption of the transmission tract at the rami bronchiales will cause a certain improvement in cardiac asthma, but not a cure since the persistent local organ net in the bronchial wall may bring about a bronchial cramp by the blood vessel route.

CARDIOSPASM

What has been said applies to cardiospasm. Proceeding with the idea that the cramp in the cardia comes through the nerve root the author developed an operation in which the anterior and the posterior branches of the vagus to the cardia are cut, first in the chest, and then at the opening of the diaphragm into the abdomen, so that no impulses can reach the cardia. This operation has not proved a complete success. It brings a transitory improvement but no cure; under special conditions the spasms again appear.

The experience gained in Raynaud's disease, in bronchial asthma and in cardiospasm make it reasonable to apply the principle in all spasmodic conditions in hollow organs that interruption of the transmission tract cannot permanently remove the spasm, since the remaining nerve elements in the local organ nets through the vascular root may bring on similar attacks.

A description of the vegetative nerves of the abdomen and pelvis led to a discussion of the surgical treatment of gastric crisis. Several different operations were proposed for the relief of gastric crisis in tabes. Hexner recommended the

sectioning of both vagi stems below the diaphragm. Laterjet and Wertheimer cut through the individual small nerves of the stomach and pylorus. Others extirpated the celiac ganglion or stretched the celiac plexus. Foerster sectioned the splanchnicus major of both sides, or the corresponding rami communicantes. All these operations are not without danger because the crisis depends on a sensory irritation which is localized in the roots of the splanchic or of the vagus, or perhaps also of the phrenic nerve. Foerster differentiated two forms of gastric crisis. In the most common form there is an abdominal visceralgia in the foreground combined with cutaneous hyperalgesia of the thoracic dermatome. In these "sympathetic crises" it is justifiable to make a resection of the thoracic roots, mainly from the seventh to the ninth, at times from the fifth to the tenth, and in some cases even from the fifth thoracic to the third lumbar. Since, after section of the posterior root, the anterior roots, as an auxiliary tract, may take over the transmission of pain, the corresponding anterior roots must also be cut. The size of the extension of the process cannot always be told beforehand. According to Foerster, the more anterior and posterior roots that are cut the better the outlook for recovery. However, the cutting of so many roots will develop a paralysis of the musculature; therefore, cutting through the anterolateral tract is to be preferred. The second form Foerster designated as the vagus crisis; it comes with unbearable nausea and marked sensitiveness over certain areas of the vagus. In these cases, section of the vagus root is indicated.

PARAVERTEBRAL INJECTIONS

Mandl employed the paravertebral injection for therapeutic purposes. In pain of the stomach the injection is made in the tenth or eleventh thoracic; in that of the kidney in the twelfth thoracic to the second lumbar, etc. When paravertebral injections are made often, it is found that blockading of a single segment will often stop the pain, although the afferent tracts of the organ go over several segments. How can this be explained? It can be said that in this case the disease process was so narrowly circumscribed that it embraced only one segment of the afferent tract. Certain observations make it plausible, however, that the relief of the pain is not brought about by the interruption of the transmission tract alone, but that another factor is to be considered. The author believes it is possible to explain it as a result of vasomotor effect. It is an old physiologic phenomenon that stimulation of sensory nerves acts on the vasomotor centers, in the sense of either pressor or depressor. It is therefore possible that through the injection an altered condition is brought about in which the afferent condition passes over centrally to the vasomotor centers. This vasomoter effect participated in the relief of the pain in the same or in the neighboring segments.

Thus, the favorable effect of partial sympathectomy is purely accidental. Results are brought about through reflex vasomotor influence, so this operation will ultimately fail in those cases in which interruption of the transmission tract is necessary; also, in paravertebral injections one must reckon with the vasomotor effect. Therefore, no positive conclusions can be drawn from the results of paravertebral injections on the innervation of the individual organs from definite cord segments. The sensory and motor centers of the individual organs must be established through trustworthy experiments in sectioning.

II. Physiology of the Peripheral Parts of the Vegetative Nervous Systems. Dr. E. Schilf.

Although the smooth muscle organs and the glands are all supplied by nerves which belong to the vegetative nervous system, they show manifold functions and structures, in contrast to the striated musculature supplied by the cerebrospinal system. The smooth muscles and the glands have one thing in common: Their activity, with slight exceptions, is involuntary, and with this there is a tendency to rhythmic movements. It is not certain whether the stimulation which incites the activity of the vegetative organs must always come through the nerve route. When, in the cat, the nerves which are concerned with the movements of the smooth pupillary muscles are cut, the pupils still dilate when the animal is greatly

excited. This is not the case when both suprarenals have previously been removed. A similar experiment can be made on the dog; when the cardiac nerves are cut and the animal is suffocated, the heart will beat faster only when both suprarenals remain. It is known that excitation produces a flow of epinephrine from the suprarenals into the blood. The epinephrine now dilates the pupils, or increases the heart rhythm. The function of the vegetative organs is, therefore, doubly regulated over the nerve route and over the blood route. By the latter type of excitation, to be called hormonal (Sharpey-Shafers, "autokoide substances"), the vegetative organ receives hormones from distant inner secretory glands over the blood route, which influence its activity. What was said about the suprarenal holds equally true for the hypophysis.

Such hormonal regulation is observed to become disturbed when the organ is permanently severed from the nervous system. Of late, vegetative nerves have often been sectioned in the belief that the organ is held in a diseased condition by increased excitation passing to the organ through the nerves. Sectioning of the nerves, however, often brought no relief. This coincides with physiologic observations that sectioning of a vegetative nerve produces only temporary paralysis in the respective organs. Soon, the normal tonus reappears and often even an increased tonus can be observed on that side. It is assumed that the organ isolated from the nerve reacts now to the substances present in the blood; it is known that vegetative organs in which the nerves are destroyed are more sensitive to epinephrine or pituitary.

In addition to this hormonal regulation, the individual organs are influenced in their activity by substances which come from their own activity or from that of the neighboring organs. These substances leave the tissues slowly to enter the circulation, so that their influence on distant lying organs is brought about through the circulation of the blood only in exceptional cases. Their activities take place generally at the site of their formation. They are mostly metabolic products which diffuse in the tissue and there exert their influence. Thus, the blood vessels will dilate in a working muscle, as a result of the substances the muscle produced during activity. Such substances are somewhat different from hormone regulations, although both contain chemical bodies in a fluid state. In vegetative nerve stimulation, also, a process takes place between the nerve and the organ, in which the stimulation is similar to that by a hormone or a chemical body. Loewi showed that on stimulation of the cardiac nerves the heart gives off specific substances which may affect the heart either as vagus or as sympathetic stimulation. Hence, in stimulation of the vegetative, nerve substances develop in the organ itself. They stimulate the organ and at the same time adjust the stimulation between the nerve and the cell. In one type of vascular dilatation, as a result of nerve stimulation by the so-called antidromic impulse, there is positive proof that the nerve stimulation sets free chemical substances which dilate the blood vessels. Thomas Lewis considered these substances to be similar to histamine.

Such a conception of the stimulation processes for nerves, in general, is supported by studies of the vegetative nerves. The slow processes of the vegetative nerves bring about a certain accumulation of stimulating substances which may be drained off, more or less, during the experiment. It is not unlikely that a similar procedure with regard to stimulation activity also takes place in the cerebrospinal nerves, except that these biologic processes proceed faster.

The vegetative nervous system is composed essentially of the sympathetic gangliated cord with its ganglia. The postganglionic fibers go from the ganglion to the organs, the smooth musculature and the glands. In addition, there is the parasympathetic nerve, supplying part of the activity of the several vegetative organs. The fibers of the parasympathetic also pass through the peripheral ganglia. Langley recognized the relation of the parasympathetic to the sympathetic. He created the conception of the autonomic nervous systems which embraces the sympathetic and the parasympathetic nerves. "Vegetative" is, therefore, synonymous with "autonomic."

The sensitiveness to nicotine of the sympathetic neurites in the ganglia is not without importance to general physiology. Langendorff showed that shortly after

the death of an animal preganglionic stimulation is without effect, but not so with postganglionic stimulation. The nerve, therefore, dies in the ganglion before it dies beyond the ganglion; recently it was shown that the ganglion is more sensitive to cold than the sympathetic nerve. These different behaviors show that the nerve in the ganglion possesses characteristics like those one knows in nerve cells.

Formerly, the vegetative system was considered a reflex center for vegetative organs, but to a reflex center belong afferent fibers that end in the sympathetic ganglion; these are not known. There must also be in the ganglion a short transmission tract leading to the efferent arc; so far, such tracts have not been found. Nor is any reflex activity known in the vegetative nervous system which is effected without the cord. There are, indeed, the so-called pseudoreflexes or axon reflexes in the vegetative nervous system, but they are certainly not true reflexes. The hyperesthesia over the skin in diseases of the inner organs may be explained on the basis of such axon reflexes. Wernoe would explain such reflex hyperesthesia of the skin, in the diseases of the inner organs, by cutaneous anemia which is brought about through axon reflexes. Here Pette's conception regarding the relation of the blood supply to the sensibility of the skin fits in.

How does the vegetative nerve differ from the cerebrospinal nerve? The rapidity of a cerebrospinal nerve excitation is about 70 milliamperes per second. There is no exact knowledge regarding the rapidity of vegetative nerve conduction. Older observations record it as much slower than the cerebrospinal. Measurements on the cervical sympathetic of the cat brought the author no definite results, since, unfortunately, autonomically innervated organs do not respond to a single stimulus, only to several successive ones. Hence, it is never known whether the reaction is due to the third or the fourth stimulus. Russian investigators have found the transmission rapidity in the nictitating membrane of the cat to be 37 cm. per second. Denning (in his investigations not yet published) found that the transmission rapidity in the autonomic nerve is much slower than that of the cerebrospinal nerve.

The fact that a vegetative nerve has a slower transmission period can be utilized in the determination whether a nerve belongs to the vegetative or the cerebrospinal system. By this method the author investigated whether the sensory visceral fibers, which undoubtedly are present in the splanchnic nerve, are sympathetic or cerebrospinal. There is no doubt that the viscera supplied by the splanchnic nerve is sensitive to pain, and that the pain is transmitted over the splanchnic. The vagus, which also supplies the viscera, carries no afferent fibers from the diaphragm down. It is reasonable to assume that the pain-carrying fibers in the splanchnic are sympathetic nerves, because the splanchnic is a sympathetic nerve. From an anatomic point of view it would also be reasonable to consider the sensory nerves of the splanchnicus as belonging to the sympathetic nervous system. But sensibility is a physiologic conception and must depend on facts. The author found that the pain fibers in the splanchnicus, as tested by its transmission rapidity, belong to the cerebrospinal system and not to the sympathetic, and Denning confirmed these results. The chronaxia of the sensory splanchnicus is exactly the same as that of a somatic nerve unlike that of a sympathetic nerve.

The author is unwilling to generalize and say that there are no sensory sympathetic fibers. So far, this has not been proved. The claim of the presence of sensory sympathetic nerves on anatomic basis has not been proved physiologically. It is not sufficient to cut all sensory cerebrospinal nerves and, if pain is still present, to conclude that the pain is transmitted over the sympathetic nerves. It must be remembered that nearly all the sympathetic nerve fibers, soon after their origin from the cord, become associated with sensory nerves of the posterior roots. There is no exact proof that there are sensory sympathetic nerves. In abdominal pain the pain is conducted in the cerebrospinal nerves which run into the splanchnic nerve.

There is a close connection between sensation and vascular innervation which is, with slight exceptions, sympathetic. Pette observed that patients in whom the sympathetic nerves were cut are subject to false sensations in the affected skin area. Braeucker also found some finer changes in the sensibility after section of the sympathetic. Pette believed it to be an alteration of function. Such an alteration could be explained by a change of the vascular supply which undoubtedly depends on section of the sympathetic. Pette's observation indicates that the receptor of the vascular supply may be influenced.

Many functions, therefore, depend indirectly on the sympathetic vascular nervous system. Since the blood vessels contract on excitation of the sympathetic nerves, they must greatly influence the activity of an organ. When the blood vessels of a working muscle contract owing to sympathetic stimulation, the muscle activity must diminish. The experimental conditions were not always the same. During muscular activity there develop in the muscle metabolic products, which may so affect it that the sympathetic nerve stimulation brings about an opposite reaction: The blood vessel does not contract, but rather dilates, on sympathetic stimulation. Such dilatation of the blood vessels may be the cause for the increased muscular activity. The observation that a muscle deprived of sympathetic nerves tires more easily also depends on changes in the vascular innervation. American investigators claim to have observed microscopically muscular twitching in the cat on stimulation of the sympathetic. Muscular contraction increases when the sympathetic is stimulated. These experiments cannot depend on vascular effects since the experiment was performed on a frog muscle that was cut away from the circulation. In addition, investigations by Magnus and Alsleben and their co-workers indicate that the sympathetic is able to inflence the cell directly.

It is possible that permeability is under the influence of the sympathetic nerve. Lebedinski showed that sympathetic stimulation alters the electrical resistance of muscles.

The experimental work on the sympathetic innervation of striated muscle has brought no definite result. The experiments were performed on a large variety of animals without considering that the results may vary with each animal. Spiegel asserted that nothing definite can be said regarding the presence of sympathetic nerve endings in striated muscles. The impression is gained that the conditions here are on a par with the teachings on internal secretions, the fundamental facts of which are known only from pathologic observations. It appears, therefore, that in certain respects one is more able to get a glimpse of the activity of the vegetative nerves from pathologic observations than by means of experimental physiology. Kure, on the basis of clinical observations, came to fruitful results which he was able to check experimentally. He showed that after cutting the sympathetic, dystrophic manifestations appear in the muscle, and he explained muscular dystrophy in man as depending on disease of the sympathetic. He also believed that rigidity can be improved by section of the sympathetic. Similar opinions had been heard for the last few years. It is always more difficult to establish facts from clinical observations than from physiologic experiments.

Stimulation of the distal end of a sectioned posterior root brings about a dilatation of the blood vessels in the corresponding area of the muscles and skin. This fact is indisputable and is contrary to Bell's idea that the posterior root contains only such nerve fibers as go to the central organ. Kure recently stated that the small myelinated fibers in the posterior roots are for the antidromic stimulation. He was able to establish histologically, by the degeneration method, that these fine fibers are not afferent, but efferent, nerves and that they transmit from the center to the periphery. Therefore, the posterior roots carry, in addition to the sensory nerves, centrifugal vasodilator nerves. This fact must be stressed, since until now it was assumed that the sensory fibers were also, at the same time, vasodilator nerves. The author, in association with Machol, showed that the nerves for the vascular dilatation of the tongue run into the chorda tympani. The chorda is composed of a similar fine myelinated nerve. When

the chorda is cut, it is possible to show the degeneration of those fine nerve fibers in the lingual nerve. Stimulation of the chorda after it has been cut produces no dilatation of the blood vessels, as would be expected if the antidromic nerve stimulation were connected with the sensory nerves. From the type of antidromic vascular dilatation it is to be concluded that there must be nerves which differ from all others known until now. When a posterior root, a cutaneous nerve or the lingual nerve is stimulated, it takes ten seconds for the vascular dilatation to set in; it may then keep up for as long as fifteen minutes. Such a result is not observed on stimulation of any other nerve. Long ago it was suspected that chemical substances are set free through the antidromic nerves causing a dilatation in the periphery. Thomas Lewis believed the substances to be similar to histamine. Histamine is a metabolic product of protein and is found in all organs.

Herpes zoster, which depends on an acute hemorrhagic process in the spinal ganglion, is in close relation with stimulation of the antidromic nerves. At the beginning the skin shows a reddening in the corresponding area in which swelling and a vesicle formation in the skin develop later. Thus, there is a relation between antidromic nerve activity, herpes zoster and cutaneous stimulation. All these activities are brought about through interrelated chemical bodies which Thomas Lewis assumed to be histamine-like. Ebbecke was of the opinion that in this way the theory of internal secretion and hormone formation expands to a general characteristic of tissue, especially of the epithelial organs. Thus, there is a nervous and chemical correlation.

Foerster's observation on the activity of the sweat glands in patients bears some relation to the histamine-like products brought on by vascular dilatation. The sweat glands are supplied only from the sympathetic, stimulation causing sweating in the corresponding area. But sweating does not take place in the dermatome, the posterior root of which is being stimulated. The skin over that area turns red, owing to stimulation of the antidromic nerve. Hara, from experiments on cats, corroborated Foerster's results. Schilf did not think that there are, in the posterior root, inhibitory nerves to the sweat glands; for it is observed that in a skin area dilated by stimulation of the antidromic nerves the blood vessels will not contract when the sympathetic is stimulated, as they always do when they are not antidromically dilated. Hence, the sympathetic vascular contractors are paralyzed.

The sweat glands also on antidromic stimulation are refractory to sympathetic stimulation. Foerster's observation is apparently only a special case of a general fact, that stimulation of an antidromic nerve produces a paralysis of the sympathetic nerves.

It was said before that substances set free in an organ may act on the vegetative system or directly on neighboring tissue. From Foerster's observations one learns that such substances may hinder sympathetic stimulation. In the activity of the vegetative nerves, there enter, therefore, hormones, metabolic products and nerve stimulating substances. These chemical substances, which, in order to be effective, must be in a fluid state, are capable of supporting the activity of the vegetative organs, but they are also able to inhibit them. Thus, the vegetative peripheral activity becomes complicated. The simple teaching that vegetative life is regulated by nerves, of which one acts as inhibitory and the other as a stimulatory, is only partly true. One and the same nerve is capable at one time to inhibit, and at another time to stimulate. Sympathetic stimulation on the uterus of the cat produces a relaxation of the muscles. When the cat is gravid, the same stimulation will produce a contraction. It cannot be said that this nerve is agonist and the other antagonist. With reference to the activities of organs, both may be agonists or antagonists. The reflex pupillary dilatation is brought about at the same time from the activity of the sympathetic and parasympathetic nerves. Which of the stimulations will be effective depends on the condition of the organs, and its humoral physiologic conditions.

III. The Physiology of the Vegetative Centers. Dr. J. P. Karplus, Vienna, Austria.

IV. Pharmacology of the Vegetative Nervous System. Dr. E. P. Pick, Vienna, Austria.

V. Pathology and Clinical Aspects of the Vegetative Nervous System. Dr. E. Frank, Breslau, Germany.

These papers will be abstracted and reported in a later number.

DISCUSSION

Dr. E. P. Pick, Vienna, Austria: I am against utilizing Kraus' and Zondek's hypothesis for pharmocologic analysis, since most known facts indicate that this hypothesis is not tenable. In addition, Frank's objection to the conception of certain vegetative centers, such as the center for water, is not sound: innumerable experiments, as well as clinical observations, cannot be explained without assuming the presence of a central localized regulation in the interbrain regardless of whether it is humoral, coming from the hypophysis or a nervous regulation. Janssen's experiments cannot be accepted as evidence of an exclusive peripheral regulation.

Dr. Laignel-Lavastine, Paris, France: The importance of the sympathetic factors (orthosympathetic, parasympathetic and metasympathetic) in the morphologic, physiologic and psychologic modalities of the individual reaction coefficients was shown on projecting slides. The sympathetic is a part of the apparatus of personality. The author divides the individual, according to the sympathetic reflexes, into five types which can be graphically presented: (1) pure vagotonic type (increased oculocardiac reflex); (2) pure hyperorthosympathetic (increased solar reflex); (3) hyperolosympathetic (increased oculocardiac and solar reflex); (4) hyposympathetic (diminution of the same reflex), and (5) normal conditions (normal physiologic fluctuations). These factors make the diagnosis easier through "concentric method" of the author. Finally, the author points out the importance of the sympathology, not only for the recognition of each personality, but also in the prophylactic and curative art of the individual reactions.

Prof. O. Foerster, Breslau, Germany: *Pupillary Innervation.*—The preganglionic fibers for the dilatation of the pupils in man run not only in the first thoracic but also in the eighth cervical and the second thoracic nerves. After extirpation of the superior cervical ganglion in man, the so-called sympathetic pupillary reaction, that is, the dilatation of the pupil on pain, is not entirely abolished, indicating that in this reaction the reflex result depends not only on a reflex stimulated innervation of the dilatators by way of the sympathetic, but partly at least also, on a reflex inhibition of the sphincter pupillae nucleus, as Karplus and Kreidl assumed to be present in the lower animal. After removal of the superior cervical ganglion the pupil does not dilate when cocaine is administered; in fact, the pupil may become somewhat contracted. The mydriasis due to atropine remains. Yet the pupil dilated by atropine does not further dilate on the administration of cocaine as is sometimes the case in the normal pupil. On the other hand, after extirpation of the superior cervical ganglion considerable dilatation of the pupil is caused by epinephrine; this is also true in those cases in which mydriasis due to epinephrine cannot be shown on the well side, and in each case the pupil will dilate more on the side of the sympathetic resection than on the unaffected side (increased susceptibility of the organ after separation of the same from the nervous system). The pupillary tract from the base of the brain to the cord passes in the anterolateral tract. In each sectioned anterolateral tract in the cervical, a Horner's symptom-complex develops on the homolateral side. This supranuclear sympathetic paralysis has this characteristic that not only does it maintain the dilatation of the pupil, on sensory stimulation, but it may even be increased, so that sometimes mild, not painful stimuli, such as the passive raising of an arm, will bring about a marked pupillary dilatation on the side of the lesion. This latter effect cannot always be demonstrated. It may be demonstrated, however, in cases of only light injury to the supranuclear tract, by throwing a light on

the pupil and, at the same time, producing a sensory stimulus, such as raising the arm or producing a painful stimulation; when this is done, the pupil on the side of the supranuclear sympathetic lesion contracts but little, much less than the pupil on the well side. Cocaine is effective in supranuclear sympathetic lesions. After a little while, the pupil on the affected side becomes dilated a little more than that on the well side.

The Innervation of the Sweat Glands.—After extirpation of the superior cervical ganglion, the sweat secretion ceases on the face, the neck and the upper thoracic area on application of heat and other sudorific medications. On the other hand, pilocarpine will cause a reaction, which apparently will even be increased on the affected side. After total section of a peripheral nerve, pilocarpine will not produce any sweat in the corresponding part. This latter fact indicates that pilocarpine does not affect the sweat gland itself. Both facts together indicate that there are, aside from the sympathetic, other parasympathetic sweat nerves that can be stimulated by pilocarpine. According to Guttmann, the latter is supplied to the face by the facial nerve. Intracranial section of the trigeminus branches does not stop the sweating of the face. A single anterior root contains preganglionic fibers for a number of cutaneous dermatomes, so that the fifth thoracic supplies dermatomes from the third to the ninth dorsal. The posterior root carries fibers, the stimulation of which inhibits sweat secretion, but essentially only for the corresponding dermatome. The position of the supranuclear sweat tract in the cord cannot be definitely established. In the anterolateral sections no noticeable hypohidrosis is found. The reflex sweating in total interruption of the spinal cord extends over all the dermatomes which are represented in the undamaged preganglionic cord segments below the lesion; it also extends considerably above, over the anesthetic line.

Vegetative Sensibility.—The gangliated cord of the sympathetic carries considerable sensory fibers, not only for the viscera but also for the extremities. Touching, especially on blunt manipulation of the lumbar gangliated cord, causes a boiling, burning pain in the leg. When the ramus communicantes of the fourth lumbar symphathetic ganglion is cut, a terrific pain appears in the inner part of the ankle. On mechanical or electric stimulation of the cervical sympathetic, marked one-sided headaches appear. The same type of headaches also appear after section underneath the superior cervical ganglion and after the caudal end of the gangliated cord is stimulated with a faradic current. This indicates that afferent fibers coming from the head go through the gangliated cord downward to the medulla. On electric stimulation of the splanchnicus major, considerable pain appears at first in the outer anterior chest wall at the sixth, seventh and eighth thoracic; on stronger stimulation, marked pain is noted in the abdomen. A similar effect is observed after section of the splanchnic and after the proximal end is stimulated electrically. The gangliated cord of the sympathetic represents an extramedullary sensory accessory conductor. In complete section of the cord, the sensation of the body metameres is not always entirely lost; this is true for the viscera, as well as for the extremities. I proved this in three cases of complete section of the cord, in one of which it was proved by autopsy and in the other two by biopsy. Filling up of the bladder could be felt by these patients, and pressing on a full bladder caused pain. Strong pressure on the tibia was felt and at times was accompanied by pain. In gastric crisis I consider the section of the anterolateral tract on the upper border from the second thoracic a relatively sure method.

Dr. H. Spatz, Munich, Germany: Results obtained from experimentation on animals lead to the assumption that definite vegetative centers are present in the brain. These centers so found are a collection of relatively small nerve cells lying near the ventricles, especially the third. The vegetative importance of the areas away from the ventricle, such as the lenticular nucleus, is at least questionable. Until now human pathology has produced less definite proof for the assumption that definite vegetative centers are present in the brain stem in the ventricular neighborhood. In the clinic, when there is a disturbance of the vegetative func-

tion, a lesion is assumed to be present in these centers. Seldom does one get undisputed postmortem evidence. It is not generally known that there is a disease in which this very ventricle lying near the center in the brain stem is almost electively pathologico-anatomically changed. That is the so-called polioencephalitis superior of Wernicke. There is hardly a disease in which the pathologic changes in both, in type as well as in its peculiar distribution, are so well characterized as in this disease which is caused mainly by the extensive use of alcohol. Not only is the gray matter around the aqueduct affected, but it is equally affected in the neighborhood of the third ventricle, especially in the area of the hypothalamus. The nucleus paraventricularis, the nuclei of the tuber cinereum and, especially, the corpora mammillaria show marked pathologic changes. It shows characteristic changes in the cells of the vascular wall and in the glia; also small hemorrhages may be present. The vegetative vagus nuclei of the fourth ventricle are also affected. The investigation of all these cases has not been concluded, but this much can be said: So far, little that is positive has been established, except the already known sleep disturbances. The lack of disturbance of heat regulation is especially to be noted. Here it is to be recalled that in Gamper's case of an encephalus, in which there was no power of the midbrain to function, the heat regulation was little disturbed. It is important to make a careful investigation of the vegetative function in cases of Wernicke's polioencephalitis. They are generally aggravated by the stuporous condition and the general deterioration of the patient. The anatomic control becomes more possible since the disease leads to a relatively early death. In my opinion, the polioencephalitis superior of Wernicke lends itself to test the truth of the present day conception regarding the significance of some centers in the midbrain for vegetative functions. To be sure, negative clinical observations are no indication that the areas in question, especially in man, do not have the significance for the metabolism assigned to them.

DR. O. MARBURG, Vienna, Austria: A common error should be corrected. Centers are always spoken of in the hypothalamus. As a matter of fact, these centers reach out more dorsally and take in a large part of the medial thalamic nuclei, and those to the cortex, on the one hand, and those to the striopallidum, on the other, are well known (corticothalamic, striopallidothalamic systems). If one admits the presence in the thalamus of only the generally recognized vasomotor centers, one can then easily conceive that it will react to psychic stimuli which come from the cortex, such as fear. But, in addition, the visual and auditory cortical centers are corticofugal, either direct or, as Brouwer has recently shown, by way of the ganglium geniculatum laterale, connecting with centers in the midbrain. Spitzer's and Spiegel's investigations show that the nucleus triangularis vestibularis is also a vegetative center, and that naturally the stimulations are activated from the cerebellovestibular centers. It can, therefore, be seen that there are a number of centers which serve the same purpose and are differentiated only in that they are activated from different sources. A comparison with the voluntary centers appears inadvisable. The vegetative centers do not appear to be superimposed, but rather to act side by side. Their difference depends only on their different sources of activation. This becomes more simple the nearer to the periphery one comes, in the cord simpler than in the thalamus. I believe, therefore, that the question of centers should be treated from this standpoint. One also knows of the caudal tracts from the thalamus, which reach their destination partly indirectly only after many interruptions. Thus, a system is found in the fasciculus longitudinalis posterior dorsalis; another is represented in the neighborhood of the aqueduct and around the ventricle, especially, the fine fibers lying near the central canal, which may be designated as the fasciculus periependimalis; and a third is apparently represented by the dorsal longitudinal bundle, which, as I, in association with Takagi, have shown, takes its origin from different sources, ends by giving off fibers at different levels at the brain stem and must surely possess vegetative function. This is in perfect accord with physiologic evidence.

Book Reviews

MIKROSKOPISCHE ANATOMIE DES VEGETATIVEN NERVENSYSTEMS. By PHILIPP STÖHR, JR. Price, 36 marks. Pp. 250, with 243 illustrations. Berlin: Julius Springer, 1928.

In the introduction the author says that anatomy alone, with its material restricted to dead tissues, cannot explain the riddles of the vegetative nervous system, and he is right in emphasizing the old rule that every productive line of experimentation must be based on a solid knowledge of anatomy. Stöhr, therefore, offers his book as an aid to any one who desires to do careful work on the sympathetic nerves, working with facts and observations, rather than with speculation and hypothesis, as experimental workers may.

He describes the difficulty of the technic necessary to stain nonmedullated nerves, endings and the like, and remarks that one must master one method and use it rather than try a new method every fortnight. He works largely with the silver stains and describes his methods carefully.

In this excellent monograph, Stöhr has succeeded in bringing before one the important features of this complicated subject in such a manner that it is not only readable but entirely understandable. He divides the whole into sympathetic and parasympathetic, and the latter into its cranial and its sacral part. The ganglia, nerve fibers and connections of each are described and illustrated. The blood vessels, lymphatic system and heart each have a chapter, while the end-organs, respiratory system, alimentary tract, excretion apparatus, genitals, skin and eyes are all separately studied. He describes the nerve along the blood vessels of the dura, the pia and the choroid plexus, and is convinced that nervous control takes part in regulating the intracranial circulation. There are also numerous nerves ending in the pia mater. Nothing is said about the vessels in the brain substance. This volume maintains the high standard of monographs published by Julius Springer; no expense is spared in illustrations on the best grade of paper. It should be in the library of every one who is interested in this increasingly important field of neurology.

DAS AUTONOME NERVENSYSTEM. By ERICH SCHILF. Leipzig: Georg Thieme, 1926.

This is a book on the physiology of the autonomic nervous system, and it is the author's aim to carry out Langley's intention of publishing another part to his "Autonomic Nervous System," which appeared in 1921. The book is therefore built on the foundation of Langley's work and is an attempt to elaborate what that author would have done had he lived.

The first part takes up the general anatomy and physiology of the oculomotor, facial, glossopharyngeal, vagus and sacral nerves, under the head of "parasympathetic." The peripheral ganglia are then discussed, and lastly the tissues which are innervated by the sympathetic nerves. There is a good discussion of smooth muscle tone, with its rhythmicity, excitability and inhibition, also its reaction to various drugs.

Part two concerns the special anatomy, the various individual organs being taken up separately. The sympathetic innervation of skeletal muscle is discussed in an interesting way. The author reviews the literature, but comes to no definite conclusion. He believes that the proof from the physiologic side is not yet good enough to base any real conclusion on, and that the histologic observations do not necessarily prove that the nerves observed are really related to muscle tone.

There is a long discussion of the innervation of the blood vessels of the different organs and of the heart. He discusses briefly the innervation of the blood vessels

of the brain. He believes with Weber that there are vasomotor nerves. The author feels that the variations in vessel caliber following injections of epinephrine indicate that there is a vasomotor control. In his discussion of intracranial pressure, he is not so clear; he speaks of only three factors: vasoconstriction, vasodilatation and the fact that "the brain possesses a resistance like every other organ from the estimation of which one may draw conclusions as to the capillary pressure of the fluid which bathes the tissue."

Since the book is concisely written and fully indexed and documented, it is not practicable to describe the whole contents. All of it is of interest to neurologists. Each organ and system is adequately discussed, and references to recent work are given. Concerning "the problem of the afferent autonomic nerves," he says that no clear proof of the presence of these nerves has yet been put forward, but he cannot say that they do not exist. He thinks that referred pain may be explained on a basis of local vasoconstriction of the skin.

There is a chapter of ten pages on the cerebral autonomic centers; the author reviews among others the work of Müller, Ranson, Karplus and Kreidl. He concludes that there is a sympathetic brain center in the region of the hypothalamus.

The book is well illustrated and is well indexed and has many and well chosen references.

DIE ZENTREN DES AUTONOMEN NERVENSYSTEMS. By E. A. SPIEGEL. Pp. 174, with 33 illustrations. Berlin: Julius Springer, 1928.

The classic investigations of Gaskell and Langley made it clear that the normal activities of the extrinsic nerves of the visceral effectors are wholly dependent on their central connections. The late recognition of this fact naturally retarded the development of knowledge of the central control of visceral functions, but at present many facts are available which show that the autonomic nerves possess fairly definite central representations. In recent years this subject has attracted some attention in clinical circles. Deficiency in meeting Claude Bernard's demand that to make a good medical observation it is necessary not only to have an observing mind, but also to be a physiologist, has led to the writing of much nonsense about the clinical aspects of autonomic functions. Therefore, it is particularly fortunate that Spiegel has written a comprehensive monograph which deals critically with the morphology and physiology of the central control of the autonomic system and with some restraint relates this subject to clinical experience.

In the introduction, some of the difficulties which beset the investigator of autonomic centers are pointed out. Analysis is complicated by the fact that the heart and the smooth muscle of certain viscera can act as independent effectors, their innervation being regulative, not indispensable, for their function. In the case of removal or impairment of a center normally responsible for a visceral state or alteration, lower centers which are normally subsidiary may take over the function of the higher level. Consequently, the effect of central ablations or lesions on such visceral organs is only temporary. Because of bilateral centers and partial crossing of descending fibers, unilateral involvements are often without obvious effects. It is always necessary to bear in mind the possibility that a visceral change may be due to an internal secretion itself liberated under the influence of an autonomic discharge. In the light of these facts it is obvious that much caution must be exercised before concluding that any particular region is the "center" for a visceral function or organ. It is not enough to show that an injury or stimulation of a definite region regularly produces a definite peripheral change. The possibility of the involvement of descending fibers from higher levels must be excluded (preferably by the method of degeneration), and finally it should be shown that such a region contains a cell group connected with preganglionic neurones.

The first chapter is devoted to the spinal cord and contains a thorough review of what is known of the visceral afferent and efferent components of the spinal roots, their central connections within the cord and with supraspinal levels. There is a good discussion of segmental localization of visceral functions. The diagnostic

importance of disturbances in pilomotor and pupillodilator functions is stressed. The reflex potentialities of the partially or wholly isolated spinal cord have led to the supposition that there are definite spinal centers for vasomotor, pilomotor and sudomotor discharges. There is no good evidence for this hypothesis, and in this and subsequent chapters one misses a definite statement that in the intact animal the cord is almost certainly only a conductor for visceral reflexes; there is no mention of Ranson's demonstration of the all-importance of the bulb in vasomotor reflexes. Without any doubt, the medulla oblongata is the part of the cerebrospinal axis most concerned with tonic and reflex discharges over autonomic fibers, and this subject is considered in the second chapter. Here are taken up the centers of the visceral components of the vagus, the centers for the secretion of saliva and tears, the vasomotor mechanism and the somewhat hypothetic center for the secretion of sweat. The visceral reflexes evoked by afferent impulses in cranial nerves are considered and shown to be largely dependent on bulbar centers. Particularly interesting are the vestibulovisceral reflexes to which Spiegel has devoted much attention. There is a critical consideration of the effects of punctures of the floor of the fourth ventricle, and the author rightly insists that the results obtained may be due to stimulation or injury of descending fibers. Evidence that visceral afferent fibers connect with the cells of Clarke's column was probably the reason for including a brief chapter on the cerebellum. The fourth chapter is devoted to the midbrain and deals with the centers of the visceral fibers of the third pair of nerves. There are sections on the light reflex and on the pathology of the Argyll Robertson pupil. The diencephalic control of visceral functions is the subject of the fifth chapter. Here, the perplexing relation of the tuber cinereum to the hypophysis is handled in all fairness, and the conclusion is drawn that the nuclei of the hypothalamus exert visceral effects partly through descending fibers and partly through secretory fibers to the hypophysis. Some evidence is presented that hypophyseal products influence the visceral centers located in the region of the third ventricle. The sympathetic discharges evoked by stimulation of the hypothalamus (Karplus and Kreidl) are considered, but the significance of this diencephalic control is not explained. A survey of possible visceral functions of the corpora striata is followed by a chapter on the relation of the projection fibers of the cortex to the autonomic outflow. The author draws the only conclusion that in the light of experimental facts can be drawn, namely, that pyramidal fibers are so related to the motor nuclei of the autonomic system that activities of skeletal muscle brought about by cortical discharge are accompanied by the appropriate visceral changes.

In the final chapter the author attempts to account for the representation of the same visceral function at several levels. He describes his own work in confirmation of the old demonstration that a bulbar mechanism suffices for the normal tonic and reflex vasomotor discharges and so disposes of the supposition that the hypothalamus maintains and regulates arterial pressure. He leaves the diencephalic representation largely unexplained; there is the suggestion that it is concerned in "psychic" activities, particularly the visceral changes attending states of waking and sleeping. There is no consideration of the emotional activation of autonomic fibers, and Cannon's important generalization that the sympathetic tends to act as a whole under conditions of stress is not mentioned. More fortunate and more in keeping with the character of the book is the omission of any reference to the ill-advised theories of vagotonia and sympathicotonia.

There is an extensive bibliography of twenty pages and an index.

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